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TOXICOLOGY AND CARCINOGENESIS STUDIES OF *N*-METHYLOLACRYLAMIDE

(CAS NO. 924-42-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *N*-METHYLOLACRYLAMIDE

(CAS NO. 924-42-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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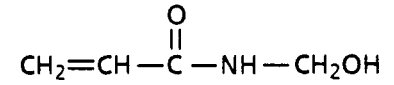
CONTENTS

APPENDIXES



N-METHYLOLACRYLAMIDE

CAS No. 924-42-5

$C_4H_7NO_2$ Molecular weight 101.1

Synonyms: *N*-(hydroxymethyl)acrylamide; *N*-(hydroxymethyl)-2-propenamide; *N*-methanolacrylamide; monomethylolacrylamide

ABSTRACT

N-Methylolacrylamide is a cross-linking agent used in adhesives, binders for paper, crease-resistant textiles, resins, latex film, and sizing agents. Toxicology and carcinogenesis studies were conducted by administering *N*-methylolacrylamide (98% pure) in water by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex for 16 days, 13 weeks, or 2 years. In vitro genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary (CHO) cells; an in vivo bone marrow micronucleus test was performed with $B6C3F_1$ mice. Neurobehavioral assays were performed during the 13-week studies.

Sixteen-Day Studies: The doses of *N*-methylolacrylamide used ranged from 25 to 400 mg/kg. All rats that received 400 mg/kg died within 4 days, and 3/5 male rats that received 200 mg/kg also died before the end of the studies. Compound-related clinical signs seen with 200 mg/kg included ataxia, muscle tremors, and hyperirritability. Ataxia after dosing was observed from day 7 to the end of the studies for rats that received 100 mg/kg. The final mean body weight of male rats that received 100 or 200 mg/kg was 10% or 27% lower than that of the vehicle controls. The final mean body weight of female rats that received 200 mg/kg was 20% lower than that of the vehicle controls. Compound-related lesions in rats included hyperplasia of the bronchiolar and tracheal epithelium, dysplasia of the nasal and tracheal epithelium, centrilobular hepatocellular necrosis, lymphoid depletion of the spleen, and myelin degeneration of the lumbar ventral spinal nerve.

All 5 male and 4/5 female mice that received 400 mg/kg *N*-methylolacrylamide died on the second day of the 16-day studies. The surviving female mouse in the 400 mg/kg group and the male and female mice in the 200 mg/kg groups were ataxic after they were dosed, starting on day 2. Weight changes were inconsistent among dose groups. Bronchial epithelial hyperplasia (mild) appeared to be dose related in males and females. Sinusoidal congestion of the liver and vacuolar degeneration of myocardial fibers were seen in males and females given 400 mg/kg.

Thirteen-Week Studies: The doses of *N*-methylolacrylamide used ranged from 12.5 to 200 mg/kg. All rats that received 100 or 200 mg/kg died before the end of the studies. Rats that received 100 or 200 mg/kg had hind limb ataxia, which progressed to hind limb paralysis. Rats that received 50 mg/kg had hind limb ataxia beginning at week 8, which progressed to hind limb paresis by week 11. The final mean body weight of rats that received 25 or 50 mg/kg was 8% or 16% lower than that of the vehicle controls for males and 6% or 10% lower for females. In neurobehavioral assessments, decreased forelimb and hind limb grip strength was seen at doses as low as 25 mg/kg for female rats and at doses as low as 12.5 mg/kg for male rats. A decreased startle response was seen for females at doses as low as 25 mg/kg. The landing foot spread was significantly increased for male and female rats that received 50 mg/kg.

Axon filament and myelin sheath degeneration of the brain stem, spinal cord, and/or peripheral nerves was seen in rats at increased incidences at 25 mg/kg and higher doses. Inflammation and/or hemorrhage and edema of the urinary bladder mucosa were seen with doses of 25 mg/kg or more in a few rats that had distended bladders at gross examination.

All mice that received 200 mg/kg *N*-methylolacrylamide died before the end of the studies. Final mean body weights of dosed and vehicle control mice were similar. A decreased relative testis weight was observed for mice that received 12.5 mg/kg or more. The relative kidney weights for male mice receiving 50 or 100 mg/kg were greater than that for vehicle controls. Neurobehavioral studies indicated decreased forelimb grip strength in male and female mice at doses as low as 25 mg/kg. An exaggerated startle response was seen for female mice given 100 mg/kg. A reduction in rotarod performance was seen for male and female mice receiving 100 mg/kg and for male mice receiving 25 mg/kg.

Hepatocellular necrosis and thymic lymphocytic necrosis were compound-related effects in mice given 200 mg/kg *N*-methylolacrylamide. Hemorrhage, necrosis, and mineralization of the zona reticularis of the adrenal gland were present in 3/10 female mice given 200 mg/kg, and cytoplasmic vacuolization of the adrenal cortex was seen with lower doses.

Based on the results of these short-term studies, 2-year studies were conducted by administering 0, 6, or 12 mg/kg *N*-methylolacrylamide in water by gavage, 5 days per week for 103 weeks, to groups of 50 rats of each sex. Groups of 50 mice of each sex were administered 0, 25, or 50 mg/kg on the same schedule.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed rats were within 6% of those of vehicle controls throughout most of the studies. Mean body weights of dosed mice were as much as 25% greater than those of vehicle controls for females and as much as 13% greater for males. The survival of female rats given 25 mg/kg per day was lower than that of vehicle controls after day 550, but survival of female rats given 50 mg/kg per day was not different from that of vehicle controls (vehicle control, 35/50; low dose, 22/50; high dose, 33/50). No differences in survival were observed between any other groups of rats or mice of either sex (male rats: 28/50; 22/50; 27/50; male mice: 30/50; 20/50; 21/50; female mice: 41/50; 35/50; 33/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: In rats, no biologically important nonneoplastic or neoplastic lesions were attributed to administration of *N*-methylolacrylamide. Higher doses might have increased the sensitivity of the studies to determine the presence or absence of a carcinogenic response.

In mice, the incidences of adenomas of the Harderian gland were increased in males given either dose of *N*-methylolacrylamide and in females given the top dose (male: vehicle control, 1/48; low dose, 14/49; high dose, 29/50; female: 5/47; 8/45; 20/48). The incidences of carcinomas of the Harderian gland were not significantly increased by *N*-methylolacrylamide administration (male: 1/48; 0/49; 2/50; female: 0/47; 3/45; 2/48).

The incidences of hepatocellular adenomas were increased in male and female mice given 50 mg/kg *N*-methylolacrylamide (male: 8/50; 4/50; 19/50; female: 3/50; 4/50; 17/49). The incidences of hepatocellular carcinomas were also marginally increased in dosed male mice (male: 6/50; 13/50; 12/50; female: 3/50; 3/50; 2/49). Hepatocellular adenomas and carcinomas (combined) occurred with positive trends, and the incidences in male and female mice receiving 50 mg/kg were increased compared with those in the vehicle controls (male: 12/50; 17/50; 26/50; female: 6/50; 7/50; 17/49).

Chronic inflammation and alveolar epithelial hyperplasia of the lung were observed at increased incidences in mice given *N*-methylolacrylamide. Sentinel mice were seropositive for Sendai virus at 18 months. The incidences of alveolar/bronchiolar adenomas (3/49; 6/50; 11/50) and carcinomas (2/49; 4/50; 10/50) were increased in male mice given 50 mg/kg. Alveolar/bronchiolar adenomas or carcinomas (combined) occurred with a positive trend in male mice (5/49; 10/50; 18/50). The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) was increased in female mice given the top dose of 50 mg/kg (6/50; 8/50; 13/49).

Ovarian atrophy was observed at increased incidences in female mice receiving *N*-methylolacrylamide (3/50; 39/45; 38/47). The incidences of benign granulosa cell tumors were also increased in the dosed groups (0/50; 5/45; 5/47).

The incidence of adenomas of the pars distalis in high dose female mice was significantly lower than that in vehicle controls (13/49; 5/14; 4/43).

Genetic Toxicology: *N*-Methylolacrylamide was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535 when tested with or without exogenous metabolic activation. *N*-Methylolacrylamide induced both sister chromatid exchanges (SCEs) and chromosomal aberrations in CHO cells with and without metabolic activation. No increase in micronucleated polychromatic erythrocytes (PCEs) was observed in the bone marrow of $B6C3F_1$ mice after intraperitoneal injection of *N*-methylolacrylamide.

Conclusions: Under the conditions of these 2-year studies, there was *no evidence of carcinogenic activity** of *N*-methylolacrylamide for male or female F344/N rats receiving doses of 6 or 12 mg/kg per day by aqueous gavage. There was *clear evidence of carcinogenic activity* of *N*-methylolacrylamide for male $B6C3F_1$ mice, based on increased incidences of neoplasms of the Harderian gland, liver, and lung. There was *clear evidence of carcinogenic activity* of *N*-methylolacrylamide for female $B6C3F_1$ mice, based on increased incidences of neoplasms of the Harderian gland, liver, lung, and ovary.

In rats, because no biologically important toxic effects were attributed to *N*-methylolacrylamide administration, somewhat higher doses could have been used to increase the sensitivity of these studies for determining the presence or absence of a carcinogenic response. In female mice, ovarian atrophy was compound related.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF *N*-METHYLOLACRYLAMIDE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 6, or 12 mg/kg *N*-methylolacrylamide in water, 5 d/wk	0, 6, or 12 mg/kg *N*-methylolacrylamide in water, 5 d/wk	0, 25, or 50 mg/kg *N*-methylolacrylamide in water, 5 d/wk	0, 25, or 50 mg/kg *N*-methylolacrylamide in water, 5 d/wk
Body weights in the 2-year study			
Dosed slightly lower than vehicle controls	Dosed slightly lower than vehicle controls	Dosed greater than vehicle controls	Dosed greater than vehicle controls
Survival rates in the 2-year study			
28/50; 22/50; 27/50	35/50; 22/50; 33/50	30/50; 20/50; 21/50	41/50; 35/50; 33/50
Nonneoplastic effects			
None	None	None	Ovarian atrophy
Neoplastic effects			
None	None	Adenomas of the Harderian gland (1/48; 14/49; 29/50); hepatocellular adenomas or carcinomas (combined) (12/50; 17/50; 26/50); alveolar/bronchiolar adenomas or carcinomas (combined) (5/49; 10/50; 18/50)	Adenomas of the Harderian gland (5/47; 8/45; 20/48); hepatocellular adenomas (3/50; 4/50; 17/49); benign granulosa cell tumors of the ovary (0/50; 5/45; 5/47); alveolar/bronchiolar adenomas or carcinomas (combined) (6/50; 8/50; 13/49)
Level of evidence of carcinogenic activity			
No evidence	No evidence	Clear evidence	Clear evidence
Genetic toxicology			
S. typhimurium (gene mutation)	CHO Cells in Vitro		Mouse Bone Marrow
	SCE	Aberration	Micronucleated PCE
Negative with and without S9	Positive with and without S9	Positive with and without S9	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of *N*-methylolacrylamide is based on 13-week studies that began in July 1981 and ended in October 1981 and on 2-year studies that began in April 1982 and ended in April 1984 at Battelle Columbus Laboratories (Columbus, OH).

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The members of the Peer Review Panel who evaluated the draft Technical Report on *N*-methylolacrylamide on October 3, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF *N*-METHYLOLACRYLAMIDE

On October 3, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of *N*-methylolacrylamide received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.R. Bucher, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats, clear evidence of carcinogenic activity for male or female mice).

Dr. Ashby, a principal reviewer, agreed with the conclusions. He said that since there was more than one tumor site supporting the level of evidence, perhaps some indication could be given regarding the tumor incidence(s) from which the category of evidence was primarily derived. Dr. Bucher replied that each tumor site was evaluated separately and the inclusion of several sites in the conclusion indicated that all fulfilled the criteria for the category specified. Dr. Ashby asked whether the presence of Sendai virus might invalidate the findings for lung tumors in mice. He also noted that the chemical seemed to be a specific clastogen, much like acrylamide, so despite a negative Ames test, *N*-methylolacrylamide should be considered to be genotoxic.

Dr. Klaassen, the second principal reviewer, agreed with the conclusions.

Dr. Popp, the third principal reviewer, agreed with the conclusions. He stated that the criteria used for dose selection for the 2-year studies in rats based on the shorter term study results were correct, even though the 2-year results indicated that higher doses could have been used. Dr. Popp also asked for clarification of the impact of Sendai virus infection on the incidence of lung tumors in mice. Dr. Bucher said that recent analysis of a large number of studies indicated no difference in the incidence of lung tumors between Sendai positive and Sendai negative control groups. This analysis also did not indicate a cocarcinogenic effect of Sendai in the induction of lung tumors by chemicals; however, a cocarcinogenic effect with *N*-methylolacrylamide could not be ruled out.

Dr. Ashby moved that the Technical Report on *N*-methylolacrylamide be accepted with the revisions discussed and with the conclusions as written for male and female rats, no evidence of carcinogenic activity, and for male and female mice, clear evidence of carcinogenic activity. Dr. Klaassen seconded the motion, which was approved unanimously by the nine panelists.

I. INTRODUCTION

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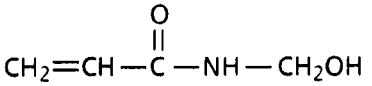


***N*-METHYLOLACRYLAMIDE**

CAS No. 924-42-5

$C_4H_7NO_2$ Molecular weight 101.1

Synonyms: *N*-(hydroxymethyl)acrylamide; *N*-(hydroxymethyl)-2-propenamide; *N*-methanolacrylamide; monomethylolacrylamide

Physical Properties, Production, and Use

N-methylolacrylamide is a stable, water-soluble, white, crystalline solid with a melting point of 74°-75° C (Feuer and Lynch, 1953). The compound was first synthesized and isolated by Feuer and Lynch by the reaction of acrylamide with paraformaldehyde in the presence of catalytic amounts of colloidal sodium. Currently, the material is available for most commercial applications as an aqueous solution (48% by weight) that contains less than 5% acrylamide (by weight) and less than 2% formaldehyde. Precise production data are not available, but the TSCA Inventory lists 12 manufacturers in the United States with a total production capacity of between 1 and 20 million pounds per year (USEPA, 1977).

N-methylolacrylamide is a bifunctional monomer possessing both vinyl and hydroxymethyl groups. Polymers of the material can be formed through the vinyl group, leaving the hydroxymethyl group free for subsequent cross-linking reactions without the need for an external cross-linker. The hydroxymethyl group also can be linked first to a substrate such as cellulose and subsequently cross-linked by free radical polymerization (American Cyanamid, 1986a). *N*-methylolacrylamide is used in adhesives and binders for paper, textiles, and nonwoven materials; in surface coatings; and in resins in varnishes, latex films, and sizing agents (American Cyanamid, 1986b). Cross-linking with *N*-methylolacrylamide is thought to impart a soft, smooth handle and crease resistance to finished cotton material (BASF, 1973). The Food and Drug Administration approves and regulates the use of *N*-methylolacrylamide in adhesives that come into contact with food (CFR, 1977). Acrylamide and related polymers cannot exceed 2% of the weight of adhesives in food packaging.

Human Exposure and Health Effects

No data on human exposure to *N*-methylolacrylamide were found in the literature. No occupational standard for exposure to this compound has been established by the Occupational Safety and Health Administration. According to the American Cyanamid Material Safety Data Sheet (American Cyanamid, 1982), nervous system disturbances may follow repeated exposure by skin contact or inhalation of dry dusts. No epidemiologic studies or case reports of human health effects from exposure to *N*-methylolacrylamide were found in the literature. No information was found on the environmental occurrence or fate of *N*-methylolacrylamide.

Short-Term Toxicity Studies

The LD_{50} values of *N*-methylolacrylamide are 0.4 g/kg for mice (oral administration) and approximately 16 g/kg for rabbits (dermal administration) (American Cyanamid, 1982). *N*-Methylolacrylamide caused mild-to-marked irritation after application of 2-16 g/kg to the skin of rabbits and after application of an unspecified amount to the eye of rabbits. Toxicity appears largely restricted to the monomer; acrylamide polymers are thought to pose little hazard to public health or to the environment (Kirk-Othmer, 1978). Barnes (1970) gave seven aqueous doses of 100 mg/kg *N*-methylolacrylamide by gavage to six rats over 12 days and followed this 2 weeks later with two doses of 200 mg/kg. The only signs of gross toxicity were fine tremors.

No signs of urine retention, an effect commonly seen in rats dosed with acrylamide, were observed when the rats were killed 37 days after the initial dose.

Acrylamide Toxicity

Almost all published toxicology studies on *N*-methylolacrylamide have compared its toxicity with that of acrylamide and various acrylamide derivatives. Acrylamide is considered to be a potent neurotoxin that shows cumulative effects (for reviews, see McCollister et al., 1964; Spencer and Schaumburg, 1974a,b; Tilson, 1981; IPCS, 1985; Miller and Spencer, 1985). A commonly seen effect of exposure to acrylamide is degeneration of distal myelinated nerve fibers, termed "dying back," but effects are also seen in the central nervous system (Tilson, 1981; Cavanagh, 1982). Inhibition of slow, retrograde axonal transport has been found to precede functional signs of neuropathy (Miller and Spencer, 1985). Acrylamide is known to react with sulfhydryl groups, and enzyme inhibition has been postulated as a mechanism for acrylamide neurotoxicity (Spencer et al., 1979). Acrylamide does not inhibit oxygen consumption by brain cortex slices or by isolated mitochondria (Hashimoto and Aldridge, 1970), but Howland et al. (1980a,b) identified a neuron-specific enolase activity that was sensitive to inhibition by acrylamide, and they also showed that acrylamide inhibited brain phosphofructokinase activity. Added glutathione was found to potentiate the acrylamide-induced enzyme inhibition in vitro, but glutathione depletion after diethylmaleate administration was associated with an earlier onset of hind limb paralysis than was seen in rats administered acrylamide only (Dixit et al., 1980a). Acrylamide dosing has also been shown to inhibit hepatic glutathione-*S*-transferase activity (Dixit et al., 1980b). Kaplan et al. (1973) suggested that acrylamide might produce toxic effects by interfering with the metabolism of pyridine nucleotides, and Tilson (1981) documented acrylamide-induced changes in dopamine receptor affinity and density in the central nervous system. Acrylamide is also a strong clastogen, as described below. Thus, acrylamide produces a variety of toxic effects, apparently through several mechanisms.

Comparative Toxicity of *N*-Methylolacrylamide and Acrylamide

Hashimoto and Aldridge (1970) determined the LD_{50} value of *N*-methylolacrylamide for male Porton rats to be 563 ± 20 mg/kg, compared with 203 mg/kg for acrylamide. Intraperitoneal injections of up to 100 mg/kg of acrylamide or *N*-methylolacrylamide twice per week resulted in onset of ataxia and weight loss at 4 weeks in the acrylamide-dosed groups, but no effects were observed after 10 weeks in the *N*-methylolacrylamide groups. However, feeding rats a diet containing 1,400 ppm *N*-methylolacrylamide for 1 week preceding acrylamide injections and 700 ppm during the week injections were administered caused an earlier onset of acrylamide toxicity than that observed in acrylamide-injected rats fed control diets. Hashimoto and Aldridge found similar rate constants for the reaction in vitro of acrylamide and *N*-methylolacrylamide, under all conditions, with glutathione, protein sulfhydryl groups, and binding to hemoglobin. The extent of depletion of nonprotein sulfhydryl groups in the brain, spinal cord, and liver was similar after gavage administration of equal amounts of acrylamide and *N*-methylolacrylamide to rats, and the pattern of tissue and subcellular organelle distribution of the carbon-14 label was similar after administration of equal doses of [1-^{14}C]acrylamide or [1-^{14}C]*N*-methylolacrylamide. Radioactivity was found in all tissues examined, with high counts in the blood. Most of the label could not be extracted with 5% trichloroacetic acid, indicating protein binding. Radioactivity was found in all subcellular fractions of brain and liver in amounts related to the protein content of the fractions. Little binding to nucleic acids was found. Reaction of sulfhydryl groups has been shown to occur with the vinyl group, which suggests that substitutions on the amide group may influence the neurotoxic effects.

Edwards (1974) reported that *N*-methylolacrylamide did produce neurotoxic effects similar to those of acrylamide, but was about one-fifth as potent, and that the neurotoxicity was probably not a result of conversion to acrylamide in vivo. Male Porton rats given diets containing 1,800 ppm *N*-methylolacrylamide for 1 week and then

diets containing 900 ppm for 5 weeks demonstrated slight ataxic effects that worsened when four additional intraperitoneal injections of *N*-methylolacrylamide at 50 mg/kg were given over the next 2 weeks (Edwards, 1975a). Tanii and Hashimoto (1983) gave male Wistar rats drinking water containing up to 13.8 mM *N*-methylolacrylamide for 90 days. They observed decreased weight gain and deficits in performance on a neurobehavioral test (rotarod). Examination of tibial and sural nerves showed microscopic evidence of shrinkage and loss of myelinated fibers, myelin retraction, and corrugated myelin sheaths. [^{3}H]Colchicine binding (a measure of neurotubulin content) was reduced by 50% in the sciatic nerve after 60 days of dosing with drinking water containing 13.8 mM *N*-methylolacrylamide. Similar effects on rotarod performance were observed for male DDY mice given doses of *N*-methylolacrylamide at one-fifth to one-half the LD_{50} value by gavage twice per week (Hashimoto et al., 1981). Neurobehavioral effects were seen after 4 weeks. Simultaneous intraperitoneal administration of 50 mg/kg phenobarbital, 5 days per week, lessened the signs of neuropathy, presumably through stimulation of drug-metabolizing enzymes.

Reproductive and Developmental Toxicity

Hashimoto et al. (1981), as part of the above-mentioned study in mice, examined effects of *N*-methylolacrylamide dosing on the testis. These studies were conducted because of the reported degeneration of the testicular tubules of rats given acrylamide (McCollister et al., 1964). Hashimoto et al. (1981) demonstrated degeneration of the epithelia of the seminiferous tubules including the spermatids and spermatocytes, reduced spermatozoa, and reduced testicular weight after 8 weeks of gavage administration (twice per week with 2.9 mmol/kg *N*-methylolacrylamide).

Sakamoto and Hashimoto (1986) reported the results from reproductive toxicity (dominant lethal) and sperm morphology tests with *N*-methylolacrylamide, acrylamide, and two other structurally related compounds (*N*-methylacrylamide and *N*-isopropylacrylamide) in DDY mice. They observed both significant increases in resorptions per dam and decreases in the number of fetuses per dam in females mated 1-8 days after exposure to males administered 4.3 mM *N*-methylolacrylamide in drinking water for 6 weeks or 1.2 mM acrylamide for 4 weeks. Administration of acrylamide also caused a reduction in the fertility of dosed males. Both acrylamide and *N*-methylacrylamide produced significant decreases in sperm count and increases in abnormal sperm morphology in males examined immediately after exposure. Reproductive toxicity was also observed with the other two acrylamide analogs.

Zenick et al. (1986) demonstrated impaired copulatory behavior of male rats given acrylamide in drinking water and increased postimplantation losses at doses that affected neurobehavioral characteristics but not the morphology of ejaculated sperm or histopathology of the testis. They also found that lower weight pups were born to females that had been exposed through drinking water for 2 weeks before they were mated with untreated males and that had been continually exposed throughout gestation and lactation. Acrylamide given to pregnant rats at doses that caused neuropathy to the dams did not affect survival, growth, or development of the pups (Edwards, 1976). Studies of acrylamide distribution outlined below have shown a marked affinity of acrylamide for spermatids.

Distribution and Metabolism

The blood concentration of *N*-methylolacrylamide decreased, with a half-life of 1.55 hours after a single 140 mg/kg intravenous dose to male Porton rats (Edwards, 1975b). Extrapolation to zero time gave a concentration close to the theoretical value for distribution in total body water. No studies on the excretion of *N*-methylolacrylamide have been reported, but with [vinyl-^{14}C]acrylamide, Miller et al. (1982) showed similar kinetics for removal from plasma, with an initial half-life of approximately 2 hours. Elimination of radioactivity from most tissues was biphasic, with a first-phase half-life of less than 5 hours and a second phase of about 8 days, although unmetabolized acrylamide could no longer be isolated from any tissue after day 1. Distribution of label was as follows: muscle, 48%; skin, 15%; blood, 12%; liver, 7%; and neural tissues, less than 1%. Only erythrocytes

concentrated radioactivity. Within 24 hours, 62% of the radioactivity was excreted in the urine; 71% was excreted within 7 days by this route. No [^{14}C]carbon dioxide was observed in expired air. Fecal excretion was minimal (6% by 7 days), but within 6 hours, 15% of the radioactivity was found in the bile, suggesting enterohepatic circulation. The major labeled material found in the urine was *N*-acetyl-*S*-(3-amino-3-oxypropyl)cysteine, a product of glutathione conjugation. The only organ that showed a somewhat delayed uptake was the testis (Miller et al., 1982). This was confirmed in whole body autoradiography studies by Marlowe et al. (1986). With acrylamide (with the vinyl moiety labeled), accumulation in the male reproductive tract peaked in the testis within 3 hours of oral dosing, and the label appeared to move subsequently to the seminiferous tubules, to the head of the epididymis, and by 9 days to the crypts of the epithelium of the glans penis. This is not consistent with labeling of spermatogonia but could represent binding to spermatids or large molecules within the seminiferous tubules. As detailed below, Shelby et al. (1986) performed a dominant lethal test with acrylamide in various strains of mice and reported increased percentages of dead implants in a time pattern consistent with effects on late spermatids and early spermatozoa.

Genetic Toxicity

N-Methylolacrylamide was not mutagenic in several strains of *Salmonella typhimurium* in either the presence or absence of exogenous metabolic activation (Hashimoto and Tanii, 1985; Zeiger et al., 1988). These results, coupled with the positive dominant lethal test in DDY mice (Sakamoto and Hashimoto, 1986; see page 14, this report) indicate an activity profile similar to acrylamide, which is an in vitro and in vivo eukaryotic mutagen whose clastogenic effect in vivo appears more pronounced in germ cells than in somatic cells (Dearfield et al., 1988). Salmonella tests with acrylamide generally indicate no mutagenic activity (Lijinsky and Andrews, 1980; Hashimoto and Tanii, 1985; Knaap et al., 1988), with one exception. Zeiger et al. (1988) reported that in one of two laboratories that tested acrylamide for mutagenicity in *S. typhimurium*, a weakly positive response was observed over a dose range of 100-10,000 µg/plate in strain TA100 in the presence of Aroclor 1254-induced male Syrian hamster liver S9. This response was not repeated in the second laboratory. Results of unpublished NTP tests in cultured Chinese hamster ovary cells showed that acrylamide induced both chromosomal aberrations and sister chromatid exchanges (SCEs) with and without exogenous metabolic activation.

Carlson and Weaver (1985) demonstrated in vivo binding of acrylamide to DNA of lung, testis, stomach, and skin of mice, 6 hours after oral or dermal administration of radiolabeled chemical. This observation is consistent with the uniformly positive in vivo genotoxicity test results with acrylamide. Acrylamide has been shown to induce dominant lethal mutations in both rats (Smith et al., 1986) and mice (Shelby et al., 1986), inherited translocations in mice (Shelby et al., 1986), and SCEs, chromosomal aberrations, and micronuclei in mouse bone marrow cells (NTP, unpublished data).

Smith et al. (1986) observed an increase in postimplantation losses in untreated Long-Evans female rats mated to males that had received 30 or 60 ppm acrylamide in drinking water for 72 days; matings with males that had received 60 ppm also resulted in increased preimplantation losses. No significant increase in chromosomal aberrations in spermatocytes was observed in males analyzed immediately or 12 weeks after completion of the breeding studies. The results indicate that acrylamide is less effective in producing clastogenic effects in spermatogenic cells than in postmeiotic sperm cells.

Shelby et al. (1986) reported induction of dominant lethal mutations in (C3H × 101)F_1 male mice mated to females of T-stock or of (SEC × C57BL6)F_1 or (C3H × 101)F_1 hybrid stock. Their studies demonstrated a peak response for an increased incidence of dead implants from matings 4.5-11.5 days after males were given a single intraperitoneal injection of 125 mg/kg; the magnitude of response was similar with T-stock and (SEC × C57BL6)F_1 females. These results indicate that late spermatids and early spermatozoa are the stages most susceptible to clastogenic damage by acrylamide. Injection of males with acrylamide at 50 mg/kg per day for 5

days (total dose of 250 mg/kg) induced approximately twice the dominant lethal effect of the single 125 mg/kg dose in matings with T-stock females, and the response with T-stock females was greater than that with (C3H × 101)F_1 hybrid females.

Shelby et al. (1987) reported positive results with acrylamide in the mouse heritable translocation test. They detected a high frequency of translocations in the offspring derived from matings performed 7-10 days postinjection between untreated (SEC × C57BL)F_1 female mice and male (C3H × 101)F_1 mice injected once per day for 5 days with 50 mg/kg acrylamide (same dosing scheme that produced over 70% dominant lethality in the previous investigations). These F_1 translocation carriers were derived from germ cells treated as late spermatids or early spermatozoa.

The induction of chromosomal aberrations in the germ cells of mice fed 500 ppm acrylamide in feed for 3 weeks is further evidence of the in vivo genetic effects of acrylamide (Shiraishi, 1978). Shiraishi was not able to demonstrate induction of chromosomal aberrations in the bone marrow cells of these same mice. However, aneuploidy and polyploidy were observed in both the bone marrow and spermatogonial cells, leading the author to suggest that acrylamide exerts at least some of its effect through disruption of cytoplasmic microtubules and spindle formation. No increase in the SCE frequency was observed in either tissue.

Subsequent studies conducted by the NTP, in which male B6C3F_1 mice were given intraperitoneal injections of 40-160 mg/kg acrylamide, demonstrated that acrylamide can induce chromosomal aberrations and SCEs, as well as micronuclei, in bone marrow cells but the response in somatic cells appeared to be less than that in germ cells (NTP, unpublished results).

Carcinogenicity

No reports of carcinogenicity studies of *N*-methylolacrylamide in animals were found in the literature. Acrylamide has been studied for carcinogenic effects in several animal species. Groups of 40 female Sencar mice were administered acrylamide by gastric intubation, by intraperitoneal injection, or topically to the shaved back in six applications over a 2-week period, with cumulative doses of 75, 150, and 300 mg/kg (Bull et al., 1984). Two weeks later, a tumor-promotion regimen was begun with 1.0 µg 12-*O*-tetradecanoyl-phorbol-13-acetate applied to the back of each animal three times per week for 20 weeks. A dose-related increased incidence of skin tumors was seen with each route of administration, and acrylamide was found to be approximately equal to urethane in potency as an initiator. These investigators also assessed the carcinogenicity of acrylamide in the strain A mouse lung bioassay. Groups of 40 male and female A/J mice were given oral doses of 6.25, 12.5, or 25 mg/kg three times per week for 8 weeks. After 9 months, the mice were killed and lung tumor incidences were evaluated. Dose-related increased incidences of lung tumors were found in the oral administration studies and also when mice were evaluated 8 months after intraperitoneal injections of 1-60 mg/kg acrylamide three times per week for 8 weeks.

In a 2-year toxicity and carcinogenicity study of acrylamide, the chemical was administered in drinking water at doses of 0, 0.01, 0.1, 0.5, or 2 mg/kg body weight (Johnson et al., 1986). In female F344 rats, increased tumor incidences were observed in the mammary gland, central nervous system, thyroid gland follicular epithelium, oral tissues, uterus, and clitoral gland; males showed increased tumors of the scrotal mesothelium, thyroid gland follicular epithelium, and central nervous system. Based on this and other information, IARC has determined that there is sufficient evidence to consider acrylamide carcinogenic in experimental animals (IARC, 1986).

Study Rationale

N-methylolacrylamide was nominated for study by the National Cancer Institute from a group of specialty chemicals used in the textile industry. Concern centered around its structural relationship to the carcinogens acetamide and acrylonitrile, and this concern was justified by the subsequent demonstration of carcinogenic effects of acrylamide. Gavage in water was chosen as the route of administration because of the high solubility of the compound in water and the dosing precision afforded by this method.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *N*-METHYLOLACRYLAMIDE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

GENETIC TOXICOLOGY

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *N*-METHYLOLACRYLAMIDE

N-Methylolacrylamide was obtained as a white, microcrystalline powder in one lot (lot no. 1-45-000) from the Gallard Schlesinger Chemical Manufacturing Corporation (Carle Place, NY). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the *N*-methylolacrylamide studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as *N*-methylolacrylamide by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared spectrum (Figure 1) was consistent with that expected for the structure and with spectra found in the literature (Sadtler Standard Spectra). The ultraviolet/visible and nuclear magnetic resonance (Figure 2) spectra were consistent with those expected for the structure of *N*-methylolacrylamide.

The purity of lot no. 1-45-000 was determined to be approximately 98% by elemental analysis, Karl Fischer water analysis, thin-layer chromatography, high-performance liquid chromatography, gas chromatography, and iodometric back titration with 0.1 N sodium thiosulfate (after bromination of the vinyl group with acidified 0.1 N aqueous bromate-bromide solution followed by the addition of excess potassium iodide solution). Thin-layer chromatography was performed with silica gel plates and a solvent system of toluene:acetone (50:50) (system 1) or chloroform:methanol (75:25) (system 2). High-performance liquid chromatography was performed with a Whatman Partisil PXS PAC column with a solvent system of methylene chloride:methanol (98.5:1.5) and detection at 240 nm. Gas chromatographic analysis was performed with flame ionization detection, a nitrogen carrier, and a 10% Carbowax 20 M column. The results of elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values. Water content was 0.11%. Bromination of the vinyl group followed by back-titration indicated a purity of 98.1%. Thin-layer chromatography by system 1 indicated a trace impurity and by system 2 indicated a trace impurity and a slight trace impurity. High-performance liquid chromatography indicated one impurity eluting before the major peak, with an area 0.21% that of the major peak. Gas chromatography indicated one impurity eluting before the major peak, with an area less than 0.1% of the major peak area. When *N*-methylolacrylamide solutions were analyzed, turbidity or undissolved particulate matter was noted. Evidence indicates that the insoluble impurity was present at less than 1% and may have been a polymer of *N*-methylolacrylamide, which would not have been detected by the analytical methods used.

Stability studies performed with the gas chromatographic system previously described indicated that *N*-methylolacrylamide was stable as a bulk chemical when kept for 2 weeks at temperatures up to 25° C. Marked decomposition of the compound was seen at 60° C. The study material was stored at 5° C at the study laboratory. No deterioration of the study material was seen over the course of the studies. The purity of the chemical at the study laboratory was monitored by gas chromatography and titration with sodium thiosulfate.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Weighed amounts of *N*-methylolacrylamide and deionized water were mixed to give the desired concentrations (Table 1). The stability of *N*-methylolacrylamide in water was determined by the gas chromatographic system previously described after dilution with methanol containing decyl alcohol as an internal standard; 1% solutions were stable when stored for 2 weeks at room temperature in the dark or when exposed for 3 hours to light and air. During the studies, *N*-methylolacrylamide/deionized water mixtures were stored at 23° C for up to 2 weeks. Subsequent stability studies specifically designed to evaluate possible formaldehyde formation during storage indicated a slow production of formaldehyde, with a maximum concentration of approximately 25 ppm in the high concentration mixture at the end of 2 weeks.

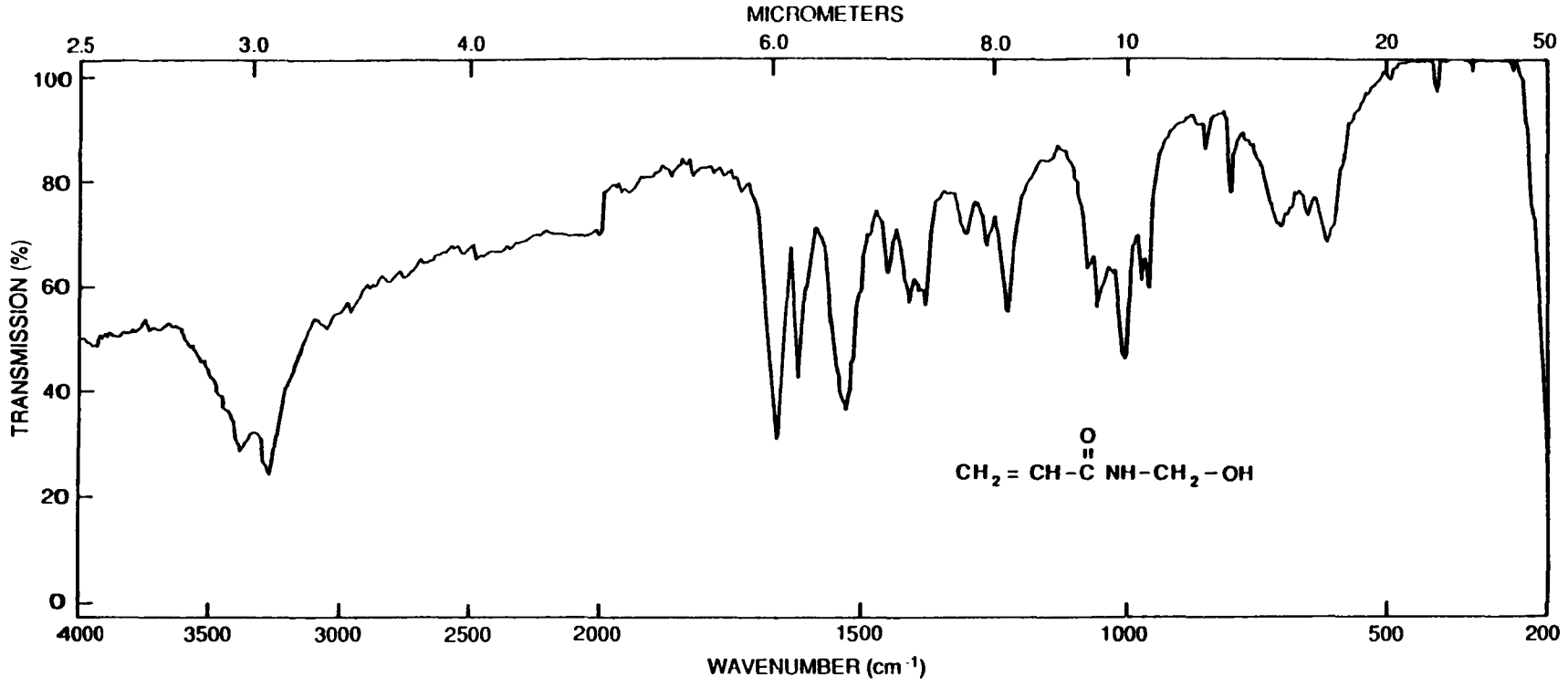


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF *N*-METHYLOLACRYLAMIDE (LOT NO. 1-45-000)

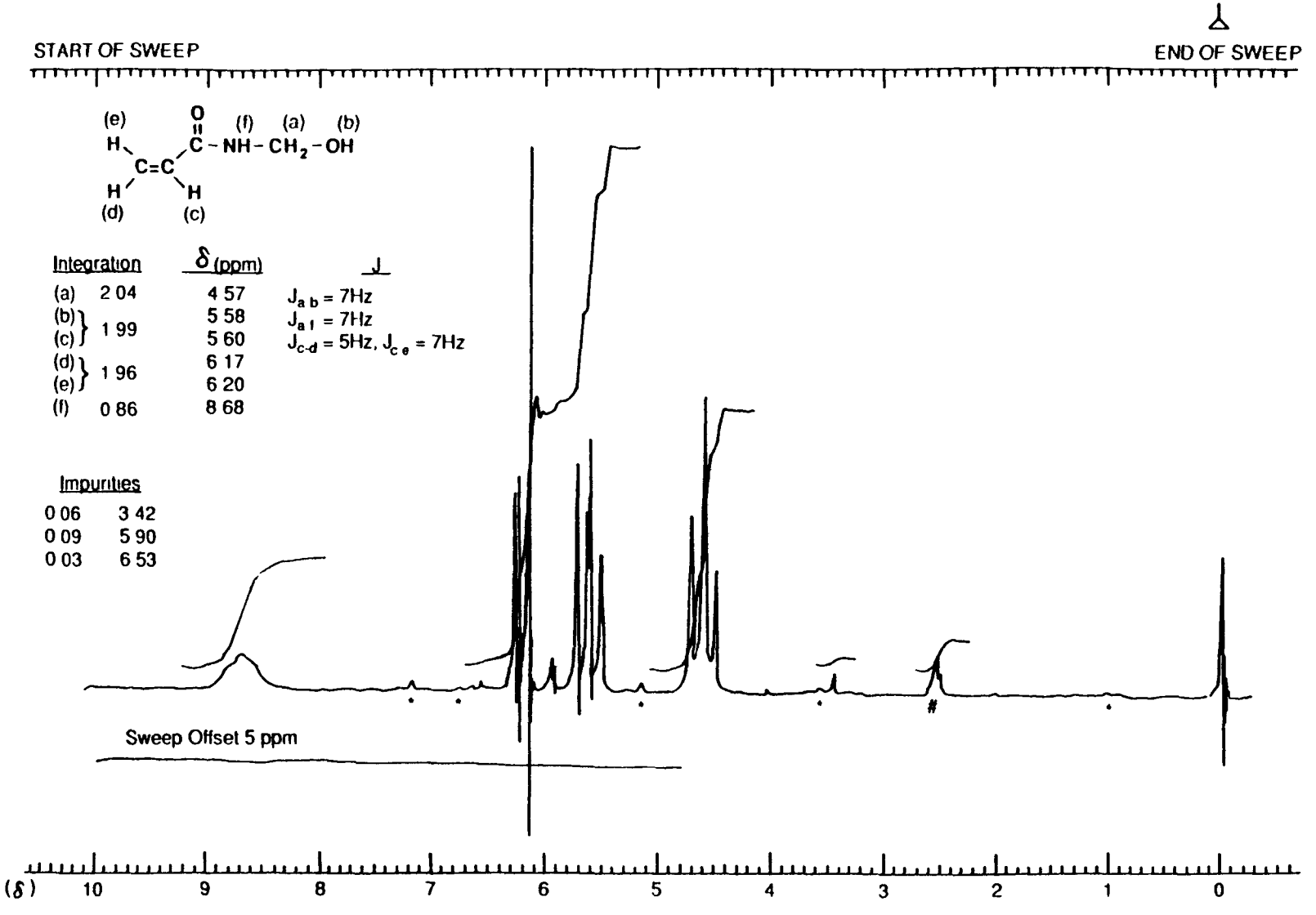


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *N*-METHYLOLACRYLAMIDE (LOT NO. 1-45-000)

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
N-methylolacrylamide was dissolved in deionized water, and serial dilutions were made for lower doses	*N*-methylolacrylamide was placed in a graduated mixing cylinder, and deionized water was added and mixed. Serial dilutions with deionized water were made for lower doses	*N*-methylolacrylamide was added to a mixing column and diluted with deionized water. The solution was mixed by inversion, and serial dilutions with deionized water were made for lower doses
Maximum Storage Time		
2 wk	2 wk	2 wk
Storage Conditions		
23° C in glass vials	23° C in glass vials	23° C in glass vials

Periodic analysis of formulated *N*-methylolacrylamide/deionized water dose mixtures was conducted at the study laboratory and the analytical chemistry laboratory. Dose mixtures were diluted with methanol containing decyl alcohol as an internal standard and analyzed by gas chromatography with a 10% Carbowax 20M-TPA column. Dose mixtures were analyzed once before the 13-week studies began and once during the 13-week studies (Table 2); the concentration of one sample differed from the target concentration by more than 10%.

During the 2-year studies, the dose mixtures were analyzed by the study laboratory at approximately 8-week intervals. All 52 mixtures analyzed were formulated to within ± 10% of the target concentrations (Table 3). Results of the periodic referee analyses performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table 4).

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Date Mixed	Concentration of *N*-Methylolacrylamide in Water for Target Concentration (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
07/07/81	2.5	2.5	98.4
	5	4.6	92.8
	10	8.9	(b) 89.1
	20	18.5	92.4
	40	37.4	93.6
07/09/81	10	10.5	(c) 104.7
08/20/81	2.5	2.6	104.0
	5	4.8	96.0
	10	9.4	94.0
	20	19.2	96.0
	40	39.1	97.8

(a) Results of duplicate analysis
(b) Out of specifications
(c) Remix

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Date Mixed	Concentration of *N*-Methylolacrylamide in Water for Target Concentration (mg/ml) (a)			
	1.2	2.4	5	10
04/12/82	1.2	2.3	--	--
04/26/82	--	--	4.7	9.4
06/14/82	1.24	2.37	4.92	10.45
(b) 08/16/82	1.16	2.25	5.06	10.02
10/19/82	1.09	2.24	4.79	10.01
12/13/82	1.09	2.14	5.16	9.80
02/07/83	1.16	2.23	4.83	9.83
04/12/83	1.12	2.24	4.72	9.26
05/31/83	1.18	2.33	5.02	10.10
08/02/83	1.21	2.22	4.60	9.33
09/19/83	1.20	2.41	4.68	9.93
11/14/83	1.24	2.44	4.91	10.24
01/09/84	1.13	2.21	4.72	9.84
03/06/84	1.20	2.39	4.83	9.82
Mean (mg/ml)	1.17	2.29	4.84	9.85
Standard deviation	0.051	0.091	0.166	0.349
Coefficient of variation (percent)	4.4	4.0	3.3	3.8
Range (mg/ml)	1.09-1.24	2.14-2.44	4.60-5.16	9.26-10.45
Number of samples	13	13	13	13

(a) Results of duplicate analysis
(b) Results of five analyses

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml) Study Laboratory (a)	Referee Laboratory (b)
04/12/82	1.2	1.15	1.15
10/19/82	2.4	2.24	2.35
04/12/83	5.0	4.72	5.07
11/14/83	10.0	10.24	9.82

(a) Results of duplicate analysis
(b) Results of triplicate analysis

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and were held for 20 days before the studies began. The rats were approximately 7 weeks old when placed on study, and the mice were 9 weeks old.

Groups of five rats and five mice of each sex were administered 0, 25, 50, 100, 200, or 400 mg/kg *N*-methylolacrylamide in deionized water by gavage 5 days per week for 12 doses over 16 days. Details of animal maintenance are presented in Table 5.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 1 and 7 and at necropsy. A necropsy was performed on all surviving animals. The liver, thymus, right kidney, heart, brain, and lungs were weighed at necropsy. Histologic examinations were performed. Groups and tissues examined are given in Table 5.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of *N*-methylolacrylamide and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and 5-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 19 or 20 days (rats) or 26 or 27 days (mice), assigned to weight classes, and distributed to cages according to a table of random numbers. Cages were assigned to groups according to another table of random numbers.

Groups of 10 rats and 10 mice of each sex were administered 0, 12.5, 25, 50, 100, or 200 mg/kg *N*-methylolacrylamide in deionized water by gavage, 5 days per week for 13 weeks. Animals were housed five per cage. Water and feed were available ad libitum. Details of animal maintenance are presented in Table 5.

Neurobehavioral tests were performed on all animals during weeks 6 and 13 of the studies. Tests performed included motor activity, forelimb/hind limb grip strength, acoustic startle reflex measurement, and landing foot spread. Grip strength was measured with a device and procedure similar to those described by Meyer et al. (1979). Auditory startle response was measured with a Respondex A Startle Monitor (Columbus Instruments, Columbus, Ohio). Landing foot spread measurements were modeled after a procedure described by Edwards and Parker (1977). Details are given in Appendix F.

Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. To determine the degree and extent of peripheral neurotoxicity of *N*-methylolacrylamide in rats during the 13-week studies, special perfusion techniques were used to examine the plantar and tibial nerves to allow fixation of the pelvic limbs without compromising organ

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 25, 50, 100, 200, or 400 mg/kg *N*-methylolacrylamide in deionized water by gavage; dose vol--5 ml/kg	0, 12.5, 25, 50, 100, or 200 mg/kg *N*-methylolacrylamide in deionized water by gavage; dose vol--5 ml/kg	Rats--0, 6, or 12 mg/kg *N*-methylolacrylamide in deionized water by gavage; mice--0, 25, or 50 mg/kg; dose vol--5 ml/kg
Date of First Dose		
Rats--4/7/81; mice--4/8/81	Rats--7/14/81-7/15/81; mice--7/21/81-7/22/81	Rats--4/19/82; mice--4/26/82
Date of Last Dose		
Rats--4/22/81; mice--4/23/81	Rats--10/12/81-10/13/81; mice--10/19/81-10/20/81	Rats--4/6/84; mice--4/13/84
Duration of Dosing		
5 d/wk; 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 16-d studies	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and then 1 × mo
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all surviving animals; tissues were examined for all animals in the 200 and 400 mg/kg groups. Tissues examined histologically for the vehicle control, 50, and 100 mg/kg groups include lungs, salivary glands, and trachea for both species and liver and nasal turbinates for rats. Organs weighed at necropsy include brain, heart, kidney (right), liver, lungs, and thymus	Necropsy performed on all animals; the following tissues examined histologically for vehicle control, 100, and 200 mg/kg groups and the 50 mg/kg rat groups: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, peripheral nerves (tibial lumbar and plantar), pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Tissues examined for lower dose groups include adrenal glands for mice and medulla, pons, nerves (sciatic, plantar, and tibial), and spinal cord for rats. Neurobehavioral tests conducted during wks 6 and 13. Organs weighed at necropsy include brain, heart, kidney (right), liver, lungs, testis (right), and thymus	Necropsy performed on all animals; the following tissues examined histologically for all vehicle control and high dose animals and all animals dying through mo 21: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, peripheral nerve, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Tissues examined for low dose animals include adrenal glands, liver, spleen, and testes for male rats; adrenal and pituitary glands for female rats; Harderian gland, liver, lungs, peripheral nerve, and stomach for male mice; and Harderian gland, liver, lungs, mammary gland, ovaries, and peripheral nerve for female mice
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification Toe clip	Toe clip	Toe and ear clip
Time Held Before Study 20 d	Rats--19-20 d; mice--26-27 d	20 d
Age When Placed on Study Rats--7 wk; mice--9 wk	Same as 16-d studies	Rats--7 wk; mice--8 wk
Age When Killed Rats--9 wk; mice--11 wk	Rats--20 wk; mice--22 wk	Rats--112 wk; mice--113 wk
Necropsy Dates Rats--4/23/81; mice--4/24/81	Rats--10/13/81-10/14/81; mice--10/20/81-10/21/81	Rats--4/18/84-4/20/84; mice--4/25/84-4/27/84
Method of Animal Distribution Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 16-d studies	Same as 16-d studies
Feed NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies
Bedding Absorb-Dri, Inc., Garfield, NJ	Same as 16-d studies	Same as 16-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 16-d studies	Same as 16-d studies
Cage Filters Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--71.6°-75.2° F; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--69.8°-73.4° F; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--65°-80° F; hum--33%-72%; fluorescent light 12 h/d; 15 room air changes/h

weights. The rats were anesthetized with sodium pentobarbital given by intraperitoneal injection, and the pelvic limbs were perfused initially with Ringer's solution for at least 1 minute followed by 4% phosphate-buffered paraformaldehyde, pH 7.2, for 12 minutes at a pressure of 160 mm mercury. Necropsy procedures for the rats were completed in the usual manner after completion of the perfusion and removal of the pelvic limbs. The sciatic, tibial, sural, and plantar nerves and tibial branches to the gastrocnemius muscle were dissected and placed in 5% phosphate-buffered glutaraldehyde, pH 7.2, for continued fixation. Segments (approximately 5 mm long) of plantar nerves taken near the bifurcation of the medial and lateral branches and sections of the small tibial branches to the gastrocnemius muscle were dehydrated through graded alcohols, placed in propylene oxide, and embedded in Epon 812. One-micron sections were stained with toluidine blue. Peripheral neurotoxicity was assessed in five rats of each sex from each dose group. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. The liver, thymus, right kidney, heart, brain, lungs, and right testis were weighed. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 6, or 12 mg/kg *N*-methylolacrylamide in deionized water by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 25, or 50 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4 weeks of age and mice at 5 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice at 8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Cages and racks were rotated. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead, unless they were missing. Some tissues were excessively autolyzed or cannibalized, and thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the studies. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or

the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Toxicology Data Management System. The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathology results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data: life table tests, logistic regression, and

Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of each dosed group with vehicle controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, this comparison of the time-specific tumor prevalence also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Zeiger et al. (1988) and Haworth et al. (1983). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, and TA1535) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in four strains. If all results were negative, the chemical was retested in all strains with a different concentration of S9. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 25, 50, 100, or 200 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive

response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

In Vivo Bone Marrow Micronucleus Test in Mice: Preliminary range-finding studies were performed to determine appropriate doses for the in vivo micronucleus test using *N*-methylolacrylamide dissolved in corn oil. Factors affecting dose selection included solubility of the chemical, animal lethality, and/or cell cycle delay induced by chemical exposure. Male mice were given two intraperitoneal injections (at 24-hour intervals) of *N*-methylolacrylamide dissolved in corn oil; the total dose volume was 0.4 ml. Solvent control animals were injected with 0.4 ml corn oil only. The positive control mice received injections of dimethylbenzanthracene. Twenty-four hours after the second injection, the mice were killed by cervical dislocation, and smears were prepared of the bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes were scored for the incidence of micronucleated cells in each of five animals per dose group. The results were tabulated as the mean ± standard error of the mean of the pooled results from all animals within a dose group.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

SIXTEEN-DAY STUDIES

All rats that received 400 mg/kg *N*-methylolacrylamide died within 4 days, and 3/5 males that received 200 mg/kg also died before the end of the studies (Table 6). Rats that received 400 mg/kg appeared to have increased motor activity and startle response. Compound-related clinical signs seen at 200 mg/kg included ataxia, muscle tremors, and hyperirritability. Ataxia after dosing was observed from day 7 to the end of the studies for rats that received 100 mg/kg. The final mean body weight of males that received 100 or 200 mg/kg was 10% or 27% lower than that of the vehicle controls. The final mean body weight of females that received 200 mg/kg was 20% lower than that of the vehicle controls.

Lesions related to *N*-methylolacrylamide administration included hyperplasia of the bronchiolar and tracheal epithelium, dysplasia of the tracheal and nasal epithelium, centrilobular hepatocellular necrosis, lymphoid depletion of the spleen, and myelin degeneration of the lumbar ventral spinal nerve (Table 7).

THIRTEEN-WEEK STUDIES

All rats that received 100 or 200 mg/kg *N*-methylolacrylamide died before the end of the studies (Table 8). Rats that received 100 or 200 mg/kg had hind limb ataxia, which progressed to hind limb paralysis. Rats that received 50 mg/kg had hind limb ataxia beginning at week 8, which progressed to hind limb paresis by week 11. The final mean body weight of rats that received 25 or 50 mg/kg was 8% or 16% lower than that of the vehicle controls for males and 6% or 10% lower for females. The relative testis weight for male rats given 50 mg/kg and the relative kidney weight for female rats given 50 mg/kg were significantly greater than those for the vehicle controls (Table 9).

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	147 ± 4	208 ± 8	+61 ± 5	
25	5/5	145 ± 4	208 ± 5	+63 ± 4	100
50	5/5	146 ± 4	205 ± 3	+59 ± 3	99
100	5/5	144 ± 4	188 ± 4	+44 ± 5	90
200	(d) 2/5	148 ± 4	152 ± 18	−3 ± 12	73
400	(e) 0/5	143 ± 5	(f)	(f)	(f)
FEMALE					
0	5/5	115 ± 5	146 ± 4	+31 ± 2	
25	5/5	113 ± 4	142 ± 6	+29 ± 3	97
50	5/5	113 ± 2	139 ± 2	+26 ± 2	95
100	5/5	112 ± 2	138 ± 2	+26 ± 3	95
200	5/5	111 ± 3	117 ± 7	+6 ± 5	80
400	(g) 0/5	112 ± 3	(f)	(f)	(f)

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 5,5; third death occurred on the day of scheduled necropsy.
(e) Day of death: all 3
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 2,3,3,3,4

TABLE 7. NUMBERS OF RATS WITH SELECTED LESIONS IN THE SIXTEEN-DAY GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

Site/Lesion	Male					Female				
	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Nose, mucosa										
Dysplasia	0	0	0	1	4	0	0	0	0	3
Trachea, mucosa										
Hyperplasia and dysplasia	0	0	1	4	5	0	0	1	4	4
Subacute inflammation	0	0	0	3	4	0	0	0	2	4
Lung										
Bronchiolar epithelial hyperplasia	0	0	2	3	3	0	0	0	3	2
Liver										
Centrilobular hepatocellular necrosis	0	0	0	1	3	0	0	0	1	4
Spleen										
Lymphoid depletion	0	--	--	1	1	0	--	--	0	2
Spinal nerve										
Myelin degeneration of the lumbar ventral nerve	0	--	--	0	2	0	--	--	0	0

(a) Five rats of each sex were examined at each dose.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
0	10/10	137 ± 2	347 ± 5	+210 ± 5	
12.5	10/10	135 ± 3	329 ± 4	+194 ± 4	95
25	10/10	142 ± 2	319 ± 5	+177 ± 6	92
50	10/10	145 ± 3	290 ± 8	+145 ± 7	84
100	(d) 0/10	136 ± 2	(e)	(e)	(e)
200	(f) 0/10	142 ± 2	(e)	(e)	(e)
FEMALE					
0	10/10	115 ± 2	206 ± 3	+91 ± 3	
12.5	10/10	113 ± 2	197 ± 4	+84 ± 5	96
25	(g) 10/10	115 ± 2	194 ± 4	+79 ± 3	94
50	(h) 10/10	113 ± 2	185 ± 4	+72 ± 4	90
100	(i) 0/10	117 ± 2	(e)	(e)	(e)
200	(j) 0/10	117 ± 1	(e)	(e)	(e)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 6,6,6,7,7,7,8,9,11,13
(e) No data are reported due to 100% mortality in this group.
(f) Week of death: 1,1,1,1,1,1,1,1,3,3
(g) One rat drowned 1 day before scheduled necropsy.
(h) Five rats drowned 1 day before scheduled necropsy.
(i) Week of death: 5,5,6,6,6,6,6,6,6,8
(j) Week of death: 1,1,1,1,1,1,2,2,3,3

TABLE 9. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg
MALE				
Number weighed (b)	10	10	10	10
Body weight (grams)	354	341	333	302
Liver	35.7 ± 0.61	38.6 ± 1.39	38.0 ± 1.34	34.1 ± 1.65
Thymus	1.0 ± 0.07	1.0 ± 0.05	1.0 ± 0.05	0.8 ± 0.04
Right kidney	3.2 ± 0.10	3.1 ± 0.11	3.2 ± 0.09	3.3 ± 0.09
Heart	2.7 ± 0.08	2.6 ± 0.03	2.6 ± 0.04	2.8 ± 0.08
Brain	5.5 ± 0.08	5.1 ± 0.57	5.8 ± 0.10	6.1 ± 0.18
Lungs	4.6 ± 0.17	4.7 ± 0.15	(c) 5.0 ± 0.31	(c) 4.9 ± 0.15
Right testis	4.1 ± 0.06	(c) 4.6 ± 0.28	4.5 ± 0.06	**4.9 ± 0.16
FEMALE				
Number weighed (b)	10	10	9	5
Body weight (grams)	207	195	196	172
Liver	31.4 ± 0.53	29.9 ± 1.15	34.5 ± 1.45	41.3 ± 10.29
Thymus	1.3 ± 0.08	1.1 ± 0.08	1.2 ± 0.06	1.3 ± 0.29
Right kidney	3.2 ± 0.09	3.3 ± 0.07	3.2 ± 0.05	*4.2 ± 0.76
Heart	3.0 ± 0.06	3.2 ± 0.06	3.1 ± 0.11	3.7 ± 0.61
Brain	9.0 ± 0.12	9.3 ± 0.24	9.2 ± 0.26	10.8 ± 1.53
Lungs	6.0 ± 0.22	(c) 6.1 ± 0.31	6.0 ± 0.20	7.5 ± 1.22

(a) Mean ± standard error in milligrams of organ per gram body weight; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Unless otherwise specified
(c) Nine animals were weighed.
*P<0.05
**P<0.01

Decreased forelimb and hind limb grip strength was seen at week 6 at the higher doses and at week 13 at doses as low as 25 mg/kg for female rats and at doses as low as 12.5 mg/kg for male rats (Table 10). A decreased startle response at 6 weeks was seen for females given 100 mg/kg and at 13 weeks at doses as low as 25 mg/kg (Table 11). The landing foot spread was significantly increased at 6 weeks for male and female rats that received 50 mg/kg. Clear hind limb paralysis was observed at higher doses. Motor activity was not consistently affected by *N*-methylolacrylamide dosing, although it appeared reduced at 6 weeks in female rats given 100 mg/kg (data on file at NTP).

TABLE 10. FORELIMB AND HIND LIMB GRIP STRENGTH FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Dose (mg/kg)	Forelimb Grip Strength				Hind Limb Grip Strength			
	Week 6		Week 13		Week 6		Week 13	
	Mean (a)	Percent of Veh. Controls	Mean (a)	Percent of Veh. Controls	Mean (a)	Percent of Veh. Controls	Mean (a)	Percent of Veh. Controls
MALE								
0	0.76 ± 0.04		0.75 ± 0.03		0.47 ± 0.02		0.45 ± 0.02	
12.5	0.76 ± 0.04	100	0.74 ± 0.03	97	0.45 ± 0.02	96	**0.37 ± 0.02	82
25	0.79 ± 0.03	104	0.69 ± 0.04	92	0.43 ± 0.02	91	**0.29 ± 0.01	64
50	0.75 ± 0.04	97	**0.50 ± 0.04	67	*0.40 ± 0.02	85	**0.16 ± 0.02	35
100	**(b) 0.32 ± 0.06	42	(c) 0.21	28	**0.12 ± 0.02	26	(c) 0.06	13
FEMALE								
0	0.73 ± 0.03		0.69 ± 0.02		0.43 ± 0.02		0.34 ± 0.02	
12.5	0.67 ± 0.03	92	0.62 ± 0.02	90	0.38 ± 0.03	88	0.32 ± 0.02	94
25	0.70 ± 0.03	96	**0.59 ± 0.03	86	0.38 ± 0.02	88	0.29 ± 0.02	85
50	*0.63 ± 0.03	86	**0.39 ± 0.02	57	**0.28 ± 0.02	65	**0.08 ± 0.01	24
100	**(d) 0.14 ± 0.02	19	(e)	(e)	**(d) 0.09 ± 0.01	19	(e)	(e)

(a) Mean ± standard error in kilograms for 10 animals; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Nine animals were examined.
(c) One animal was examined; not included in statistical evaluation.
(d) Six animals were examined.
(e) No animals in this group were alive at the time of the test.
*P<0.05
**P<0.01

TABLE 11. AUDITORY STARTLE RESPONSE AND LANDING FOOT SPREAD FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

Dose (mg/kg)	Auditory Startle Response		Landing Foot Spread	
	Week 6	Week 13	Week 6	Week 13
MALE				
0	608 ± 24	447 ± 28	72 ± 2.8	75 ± 3.5
12.5	554 ± 40	453 ± 58	71 ± 2.5	79 ± 2.5
25	641 ± 59	355 ± 39	71 ± 3.8	88 ± 5.1
50	523 ± 64	383 ± 41	*85 ± 3.8	(b)
100	**(c) 307 ± 37	(d)	(b)	(b)
FEMALE				
0	628 ± 29	466 ± 25	55 ± 3.5	58 ± 1.6
12.5	641 ± 36	418 ± 33	59 ± 3.8	62 ± 2.2
25	607 ± 45	*348 ± 28	58 ± 2.5	63 ± 3.2
50	659 ± 28	**288 ± 42	**73 ± 3.2	(b)
100	**(e) 279 ± 31	(d)	(b)	(d)

(a) Mean ± standard error in millimeters for landing foot spread and in units of auditory startle response for 10 animals; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Not testable because of hind limb paralysis
(c) Nine animals were examined.
(d) No animals in this group were alive at the time of the test.
(e) Six animals were examined.
*P<0.05
**P<0.01

Axon filament and myelin sheath degeneration of the brain stem, spinal cord, and/or peripheral nerves was seen at increased incidences at 25 mg/kg and higher (Table 12). Brain lesions in high dose rats consisted primarily of degeneration and cellular necrosis in the granular cell layer of the cerebellum. Spinal cord lesions were limited to the white matter and consisted of shrunken or dilated axons, many of which were missing the axon filament. Peripheral nerve lesions consisted of degenerative changes of varying degrees in the myelin, including internal myelin blebs, myelin clumping, segmental axonal swelling, the presence of giant axonal fibers, and increased interstitial stroma. The brain and spinal cord were examined using the customary 5-μm paraffin sections stained with hematoxylin and eosin. The no-effect level was determined to be 25 mg/kg with this procedure. Peripheral nerves were examined after perfusion fixation, preparation of 1-μm sections of plastic-embedded tissues, and staining with toluidine blue. With this technique, the no-effect level was determined to be 12.5 mg/kg.

Inflammation and/or hemorrhage and edema of the mucosal cells lining the urinary bladder were seen in 1/10 males at 25 mg/kg, 3/10 females at 50 mg/kg, 5/10 males and 1/10 females at 100 mg/kg, and 1/10 females at 200 mg/kg. These lesions were seen in rats whose urinary bladders appeared distended upon gross examination.

Dose Selection Rationale: Because of increased nervous system lesions and the degree of neurobehavioral changes observed at 25 mg/kg and above, doses selected for rats for the 2-year studies of *N*-methylolacrylamide were 6 and 12 mg/kg, administered in water by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 6%-7% lower than those of vehicle controls after week 94 (Table 13 and Figure 3). Mean body weights of high dose female rats were 5%-6% lower than those of vehicle controls after week 98. No compound-related clinical signs were observed.

TABLE 12. NUMBER OF RATS WITH NERVOUS SYSTEM LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

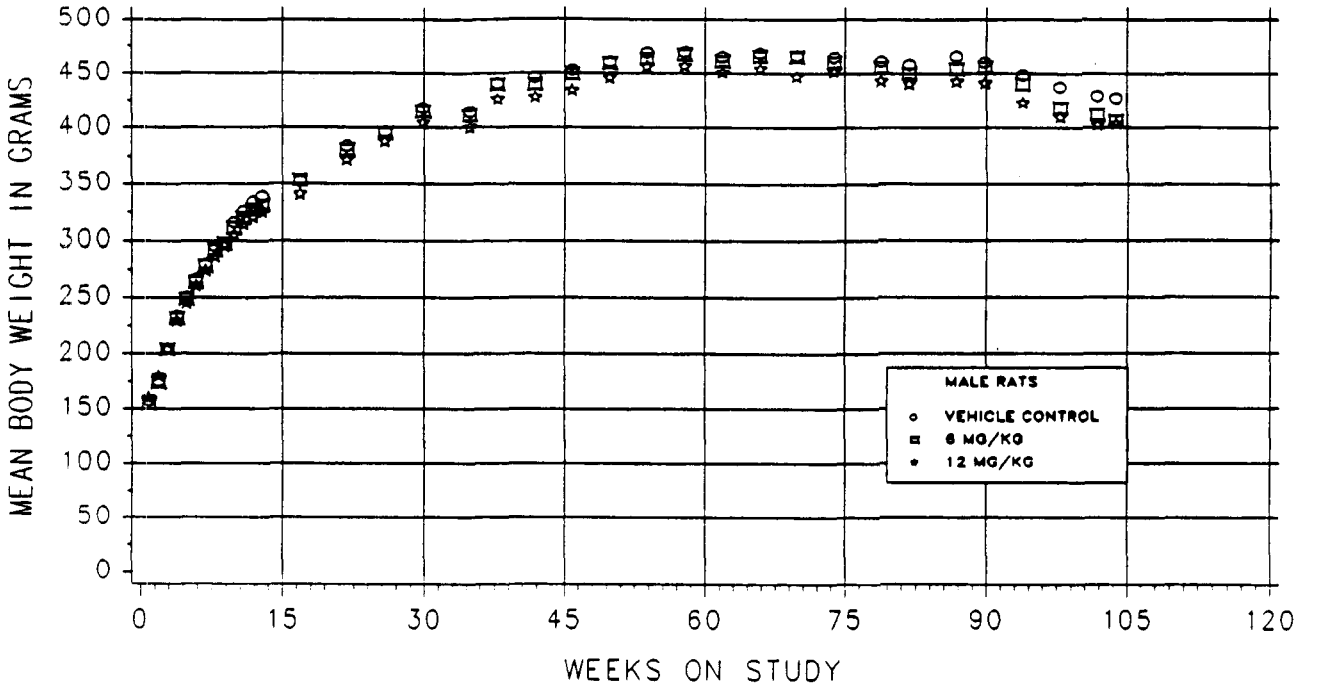
Dose (mg/kg)	Male	Female
0	1	1
12.5	0	0
25	4	2
50	10	10
100	9	10
200	4	7

(a) Ten animals were examined per group (9 per group for 25 mg/kg); lesions observed included axon filament and myelin sheath degeneration of the brain stem, spinal cord, and/or peripheral nerves.

TABLE 13. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Week on Study	Vehicle Control		6 mg/kg			12 mg/kg		
	Av. Wt. (grams)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed
MALE								
1	159	50	156	98	50	161	101	50
2	177	50	175	99	50	181	102	50
3	206	50	205	100	50	205	100	50
4	235	50	233	99	50	230	98	50
5	252	50	250	99	50	246	98	50
6	268	50	265	99	50	261	97	50
7	281	50	279	99	50	275	98	50
8	297	50	293	99	50	287	97	50
9	300	50	299	100	50	296	99	50
10	318	50	313	98	50	306	96	50
11	327	50	322	98	50	316	97	50
12	335	50	329	98	50	322	96	50
13	340	50	332	98	50	327	96	50
17	353	50	354	100	50	341	97	50
22	385	50	382	99	50	373	97	50
26	398	50	397	100	50	389	98	50
30	419	50	416	99	50	406	97	50
35	416	50	412	99	50	401	96	50
38	442	50	441	100	50	427	97	50
42	448	50	441	98	50	429	96	50
46	454	50	451	99	50	435	96	50
50	462	50	461	100	50	447	97	50
54	471	50	465	99	50	457	97	49
58	471	50	468	99	49	458	97	49
62	467	48	463	99	47	452	97	48
66	470	48	467	99	47	455	97	48
70	468	48	466	100	47	454	97	47
74	470	47	465	99	43	453	96	47
79	463	46	458	99	43	445	96	47
82	460	45	452	98	40	442	96	45
87	467	43	459	98	35	444	95	44
90	462	42	457	99	34	442	96	43
94	450	40	442	98	32	424	94	40
98	439	36	420	96	30	411	94	39
102	433	31	414	96	25	404	93	33
104	429	29	408	95	24	405	94	29
FEMALE								
1	124	50	123	99	50	123	99	50
2	134	50	131	98	50	131	98	50
3	147	50	143	97	50	142	97	50
4	159	50	155	97	50	155	97	50
5	164	50	161	98	50	160	98	50
6	170	50	167	98	50	166	98	50
7	176	50	173	98	50	171	97	50
8	180	50	176	98	50	175	97	50
9	183	50	179	98	50	180	98	50
10	188	50	183	97	50	184	98	50
11	188	50	184	98	50	185	98	50
12	192	50	188	98	50	188	98	50
13	194	50	190	98	50	189	97	50
17	202	50	194	96	50	197	98	50
22	211	50	204	97	49	206	98	50
26	217	50	212	98	49	209	96	50
30	224	50	220	98	49	217	97	50
35	224	50	220	98	49	217	97	50
38	236	50	229	97	49	229	97	50
42	245	50	237	97	49	237	97	50
46	250	50	244	98	48	243	97	50
50	260	50	255	98	48	251	97	50
54	270	49	266	99	48	260	96	50
58	278	48	271	97	48	269	97	49
62	279	48	268	96	(a) 46	268	96	49
66	285	48	278	98	44	277	97	48
70	293	48	282	96	44	287	98	48
74	299	48	289	97	43	290	97	48
79	302	47	287	95	41	293	97	48
82	305	47	294	96	39	294	96	47
87	317	46	303	96	36	305	96	44
90	321	45	305	95	35	314	98	42
94	324	44	305	94	32	313	97	(a) 39
98	322	41	305	95	28	307	95	39
102	324	37	311	96	24	306	94	38
104	322	36	309	96	23	307	95	34

(a) The number of animals weighed was lower than the number of animals surviving.



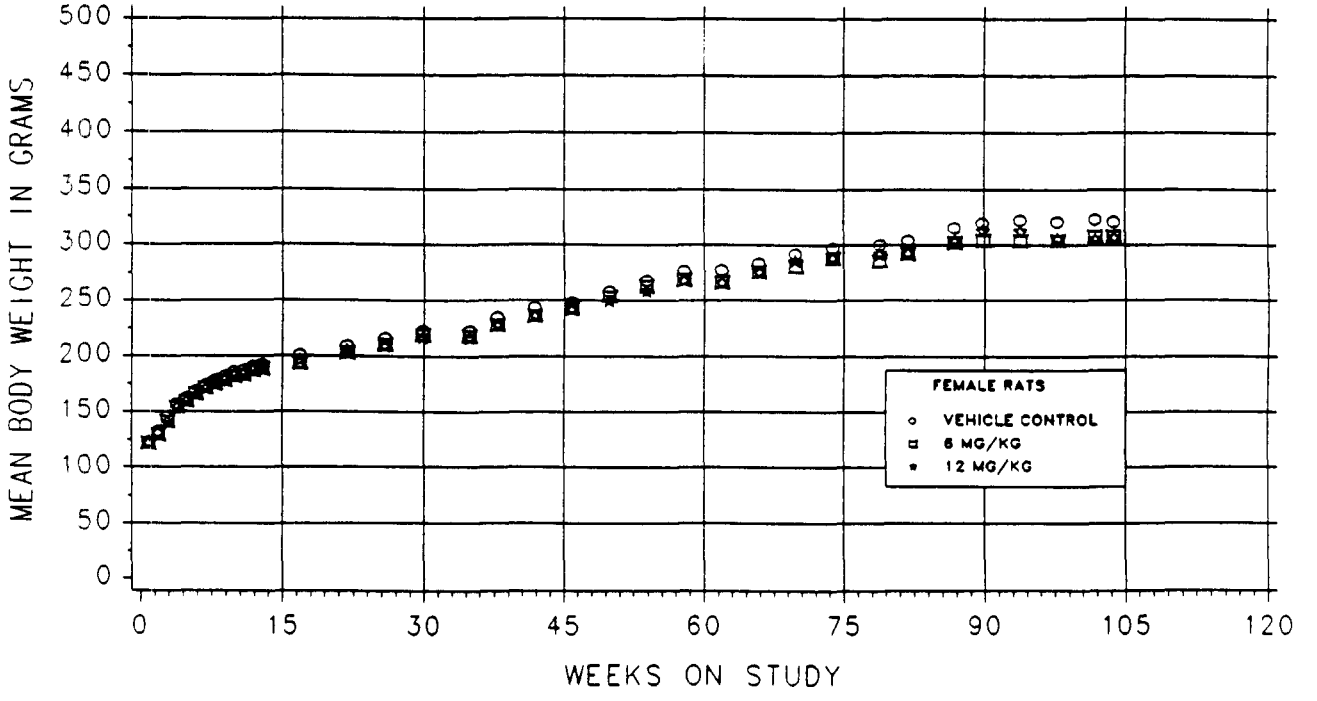


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED *N*-METHYLOLACRYLAMIDE IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered *N*-methylolacrylamide at the doses used in these studies and for vehicle controls are shown in Table 14 and in the Kaplan and Meier curves in Figure 4.

The survival of low dose female rats was significantly lower than that of vehicle controls after day 550. No significant differences in survival were observed between any other groups of either sex.

TABLE 14. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	6 mg/kg	12 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	7	7	4
Moribund kills	15	22	19
Animals surviving until study termination	28	(b) 22	27
Survival P values (c)	0.964	0.226	0.910
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	5	8	5
Moribund kills	10	20	12
Animals surviving until study termination	35	22	33
Survival P values (c)	0.747	0.007	0.788

(a) First day of termination period: 731
(b) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

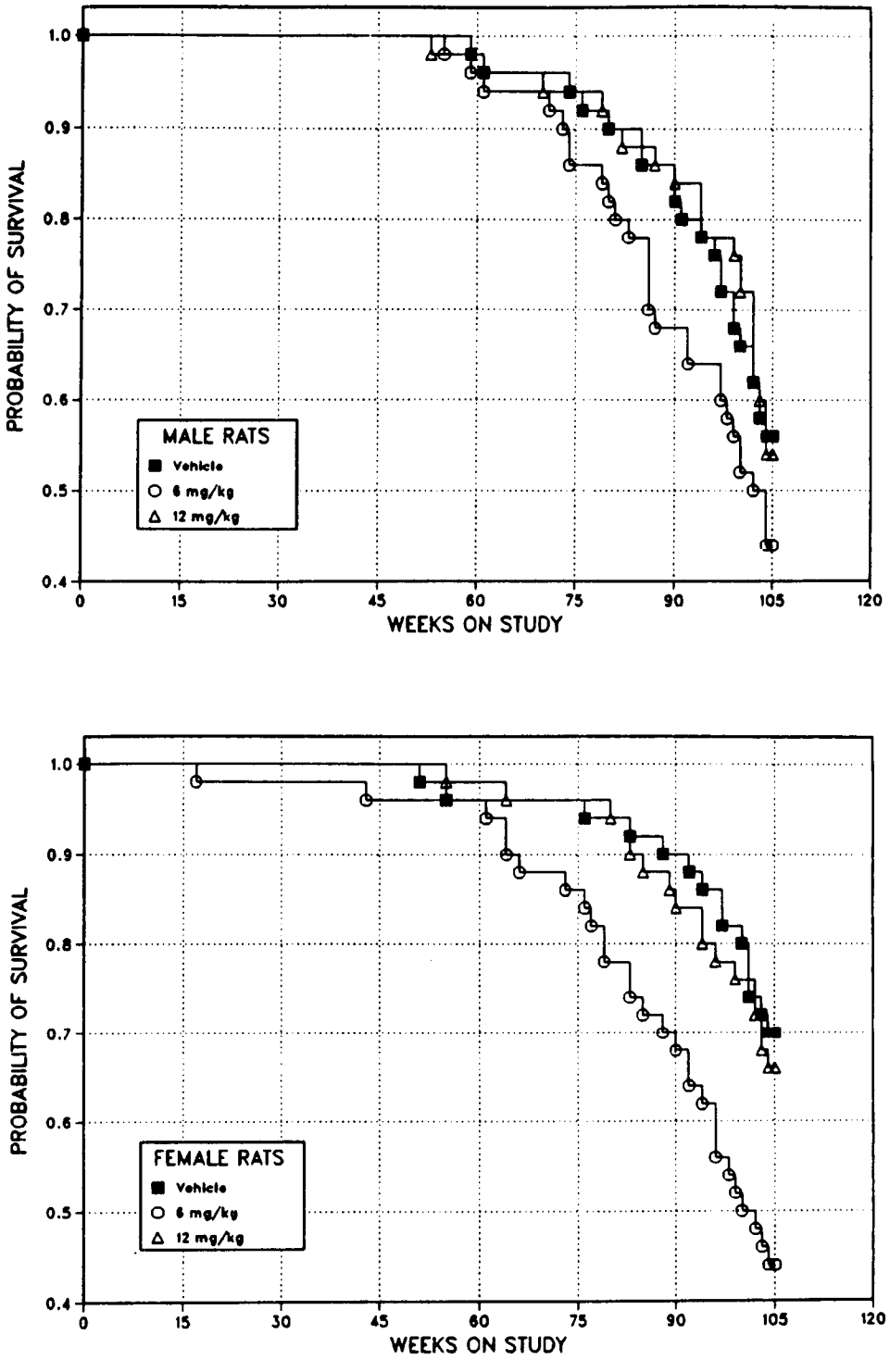


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED *N*-METHYLOLACRYLAMIDE IN WATER BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the skin, testis, and liver.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Skin: The incidence of keratoacanthomas in male rats given the low dose of *N*-methylolacrylamide was significantly greater than that in the vehicle controls (vehicle control, 1/50; low dose, 6/50; high dose, 3/50). The combined incidences of skin neoplasms (basal cell adenomas, basosquamous tumors, keratoacanthomas, squamous papillomas, or sebaceous adenomas) (5/50; 8/50; 5/50) were not increased in dosed male rats.

Testis: The incidence of interstitial cell adenomas was increased in high dose male rats (vehicle control, 40/50; low dose, 41/48; high dose, 46/50). This increase was not considered biologically significant, since these tumors generally appear in nearly all male F344/N rats in 2-year studies.

Liver: Cystic degeneration was observed at a marginally increased incidence in high dose male rats (male: vehicle control, 10/50; low dose, 8/50; high dose, 19/50; female: 0/50; 0/21; 2/50). Neoplastic nodules and neoplastic nodules or hepatocellular carcinomas (combined) in male rats occurred with significant negative trends; the incidences in the dosed groups were not significantly different from those in the vehicle controls (neoplastic nodules or hepatocellular carcinomas, combined: vehicle control, 4/50; low dose, 2/50; high dose, 0/50).

III. RESULTS: MICE

SIXTEEN-DAY STUDIES

All males and 4/5 females that received 400 mg/kg *N*-methylolacrylamide died within 24 hours of being dosed (Table 15). No other compound-related deaths occurred. The surviving female in the 400 mg/kg group and the males and females in the 200 mg/kg groups were ataxic after they were dosed, starting on day 2. Weight changes could not be interpreted because the final mean body weight of vehicle control male mice was lower than the initial weight, and the initial mean weight of the vehicle control female mice was about 3 g lower than those of the dosed groups.

Bronchial epithelial hyperplasia (mild) was seen in 4/5 males and 2/5 females given 400 mg/kg *N*-methylolacrylamide, in 2/5 males and 2/5 females given 200 mg/kg, and in 1/5 male and 1/5 female vehicle controls. Sinusoidal congestion of the liver was seen in 5/5 males and 3/5 females receiving 400 mg/kg. In the heart, vacuolar degeneration of the myocardial fibers was seen in 1/5 males and 2/5 females given 400 mg/kg.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	23.4 ± 0.2	23.2 ± 0.4	−0.2 ± 0.2	
25	5/5	24.0 ± 0.5	24.0 ± 0.5	0.0 ± 0.3	103.4
50	5/5	24.2 ± 0.7	24.2 ± 0.7	0.0 ± 0.0	104.3
100	5/5	24.4 ± 0.2	25.0 ± 0.3	+0.6 ± 0.4	107.8
200	5/5	22.8 ± 0.4	25.8 ± 0.4	+3.0 ± 0.3	111.2
400	(d) 0/5	23.8 ± 0.6	(e)	(e)	(e)
FEMALE					
0	5/5	16.4 ± 0.4	21.2 ± 0.4	+4.8 ± 0.2	
25	5/5	19.0 ± 0.3	21.2 ± 0.4	+2.2 ± 0.2	100.0
50	5/5	19.6 ± 0.2	21.4 ± 0.6	+1.8 ± 0.6	100.9
100	(f) 4/5	17.2 ± 0.9	20.0 ± 1.2	+2.3 ± 0.5	94.3
200	5/5	19.2 ± 0.2	21.2 ± 0.5	+2.0 ± 0.3	100.0
400	(d) 1/5	19.6 ± 0.2	21.0 ± 0.0	+1.0 ± 0.0	99.1

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: all 2
(e) No data are reported due to 100% mortality in this group.
(f) Day of death: 8

THIRTEEN-WEEK STUDIES

All mice that received 200 mg/kg died within 5 weeks (Table 16). One of 10 males that received 100 mg/kg, 1/10 males that received 50 mg/kg, and 1/10 male vehicle controls also died as a result of possible gavage error. Hind leg paresis was observed in the high dose mice, starting during the second week of the studies. Final mean body weights of dosed and vehicle control mice were similar. A decreased relative testis weight was observed for male mice that received 12.5 mg/kg or more (Table 17). The relative kidney weights for male mice at 50 and 100 mg/kg were significantly greater than that for the vehicle controls. Changes in other organs did not appear biologically significant.

Dose-related decreases in forelimb grip strength were seen at weeks 6 and 13 in male and female mice given doses of *N*-methylolacrylamide as low as 25 mg/kg, and decreases in hind limb grip strength were also seen in males and females at week 13 at doses as low as 25 mg/kg (Table 18). An exaggerated startle response was seen at week 13 for female mice receiving 100 mg/kg, but changes at other doses and times were inconsistent (Table 19). A reduction in rotarod performance was seen at week 6 for male and female mice receiving 100 mg/kg and for male mice receiving 25 mg/kg (Table 20). Performance at 13 weeks was not significantly reduced for dosed mice compared with that for vehicle controls. Motor activity measures were not significantly different for dosed and vehicle control mice (data on file at NTP).

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	22.8 ± 0.4	30.4 ± 0.8	+7.6 ± 0.7	
12.5	10/10	22.9 ± 0.5	28.5 ± 1.2	+5.6 ± 0.9	93.8
25	10/10	23.2 ± 0.2	30.6 ± 0.8	+7.4 ± 0.7	100.7
50	(d) 9/10	23.5 ± 0.3	30.2 ± 0.6	+6.6 ± 0.4	99.3
100	(d) 9/10	22.8 ± 0.2	30.0 ± 0.4	+7.2 ± 0.5	98.7
200	(e) 0/10	22.9 ± 0.3	(f)	(f)	(f)
FEMALE					
0	10/10	19.4 ± 0.4	25.9 ± 0.4	+6.5 ± 0.4	
12.5	10/10	19.9 ± 0.3	26.1 ± 0.8	+6.2 ± 0.6	100.8
25	10/10	19.5 ± 0.3	26.3 ± 0.9	+6.8 ± 0.6	101.5
50	10/10	19.9 ± 0.3	26.6 ± 0.9	+6.7 ± 0.8	102.7
100	10/10	20.3 ± 0.4	26.1 ± 0.4	+5.8 ± 0.4	100.8
200	(g) 0/10	19.1 ± 0.2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death due to gavage error
(e) Week of death: 1,1,1,1,2,3,5,5,5,5
(f) No data are reported due to 100% mortality in this group.
(g) Week of death: 1,2,2,2,3,4,4,5,5,5

TABLE 17. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
MALE					
Number weighed	9	10	10	9	9
Body weight (grams)	30.4	30.4	32.3	31.6	30.9
Liver	54.5 ± 1.44	52.6 ± 0.57	*59.0 ± 1.48	55.8 ± 1.55	56.3 ± 0.81
Thymus	1.4 ± 0.15	1.2 ± 0.10	1.0 ± 0.09	1.2 ± 0.08	1.3 ± 0.09
Kidney	9.2 ± 0.32	9.3 ± 0.21	10.0 ± 0.33	*10.2 ± 0.22	**10.5 ± 0.12
Heart	5.0 ± 0.31	4.6 ± 0.07	5.0 ± 0.18	5.0 ± 0.20	4.7 ± 0.17
Brain	15.5 ± 0.44	14.6 ± 0.43	**13.8 ± 0.30	14.5 ± 0.26	14.7 ± 0.30
Lungs	8.0 ± 0.41	8.0 ± 0.36	8.6 ± 0.30	8.0 ± 0.37	8.6 ± 0.46
Right testis	4.0 ± 0.11	*3.6 ± 0.12	**3.3 ± 0.09	**3.3 ± 0.06	**2.5 ± 0.06
FEMALE					
Number weighed (b)	10	10	10	10	10
Body weight (grams)	26.4	25.5	25.8	26.5	26.4
Liver	52.4 ± 0.87	49.2 ± 1.52	49.8 ± 1.19	50.4 ± 0.78	**57.8 ± 0.88
Thymus	1.8 ± 0.11	(c) 1.5 ± 0.16	1.6 ± 0.04	1.7 ± 0.14	1.6 ± 0.09
Kidney	7.5 ± 0.20	8.0 ± 0.15	7.7 ± 0.15	8.0 ± 0.20	7.9 ± 0.09
Heart	4.5 ± 0.19	4.9 ± 0.12	4.7 ± 0.18	4.7 ± 0.21	5.0 ± 0.20
Brain	18.1 ± 0.55	18.6 ± 0.50	18.5 ± 0.56	17.8 ± 5.81	17.6 ± 0.50
Lungs	8.7 ± 0.29	(c) 8.8 ± 0.28	9.1 ± 0.57	8.4 ± 0.26	9.0 ± 0.33

(a) Mean ± standard error in milligrams of organ per gram body weight; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Unless otherwise specified
(c) Nine animals were weighed.
*P<0.05
**P<0.01

TABLE 18. FORELIMB AND HIND LIMB GRIP STRENGTH FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

	Forelimb Grip Strength				Hind Limb Grip Strength			
	Week 6		Week 13		Week 6		Week 13	
Dose (mg/kg)	Mean (a)	Percent of Veh. Controls	Mean (a)	Percent of Veh. Controls	Mean (a)	Percent of Veh. Controls	Mean (a)	Percent of Veh. Controls
MALE								
0	138 ± 5.7		143 ± 5.4		80 ± 3.8		68 ± 4.4	
12.5	123 ± 5.7	89	128 ± 4.1	90	71 ± 6.6	89	66 ± 4.1	97
25	**113 ± 4.4	82	**120 ± 5.1	84	66 ± 5.7	82	**48 ± 3.8	70
50	**102 ± 3.5	74	**(b) 113 ± 3.7	79	63 ± 6.6	79	**(b) 45 ± 4.0	66
100	**(b) 114 ± 3.2	83	(b) 131 ± 4.7	92	**43 ± 5.1	54	**32 ± 2.2	47
FEMALE								
0	122 ± 4.4		129 ± 3.5		54 ± 2.8		49 ± 1.9	
12.5	111 ± 4.4	91	**114 ± 4.1	88	49 ± 3.5	91	42 ± 2.2	86
25	**101 ± 3.2	83	**112 ± 4.4	87	46 ± 1.9	85	*40 ± 3.5	82
50	**94 ± 3.2	77	**100 ± 3.2	78	45 ± 3.5	83	**36 ± 2.2	73
100	**99 ± 3.2	81	**111 ± 4.7	86	**26 ± 3.5	46	**29 ± 1.9	59

(a) Mean ± standard error in grams for 10 animals; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Nine animals were examined.
*P< 0.05
**P<0.01

TABLE 19. AUDITORY STARTLE RESPONSE FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

Dose (mg/kg)	Week 6	Week 13
MALE		
0	398 ± 54	(b) 257 ± 40
12.5	332 ± 37	228 ± 51
25	339 ± 34	237 ± 17
50	388 ± 44	(b) 260 ± 31
100	(b) 363 ± 45	(b) 200 ± 43
FEMALE		
0	284 ± 39	192 ± 27
12.5	325 ± 41	231 ± 21
25	363 ± 46	292 ± 52
50	385 ± 43	266 ± 22
100	291 ± 32	**409 ± 59

(a) Mean ± standard error in units of auditory startle response for 10 animals
(b) Nine animals were examined.
**P<0.01 vs. the vehicle controls by Dunnett's test (Dunnett, 1955)

TABLE 20. ROTAROD PERFORMANCE FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Dose (mg/kg)	Week 6 Mean (seconds)	Week 6 Median (seconds)	Week 6 Number (a)	Week 6 Percent	Week 13 Mean (seconds)	Week 13 Median (seconds)	Week 13 Number (a)	Week 13 Percent
MALE								
0	120 ± 0	120	10/10	100	(b) 120 ± 0	120	9/9	100
12.5	97 ± 40	120	7/10	70	97 ± 38	120	7/10	70
25	85 ± 43	120	(c) 5/10	50	100 ± 29	120	6/10	60
50	102 ± 40	120	8/10	80	(b) 118 ± 6	120	8/9	89
100	(b) 72 ± 41	58	(c) 3/9	33	(b) 84 ± 45	120	5/9	56
FEMALE								
0	120 ± 0	120	10/10	100	113 ± 23	120	9/10	90
12.5	120 ± 0	120	10/10	100	112 ± 25	120	9/10	90
25	120 ± 0	120	10/10	100	117 ± 10	120	9/10	90
50	120 ± 0	120	10/10	100	99 ± 35	120	7/10	70
100	67 ± 47	74	(c) 3/10	30	90 ± 42	120	6/10	60

(a) Number of mice achieving 120 seconds rod time/number of mice tested
(b) Nine animals were examined.
(c) Significantly different from vehicle control proportion by the chi-square test (P<0.05)

Hepatocellular necrosis was observed in 6/10 males and 2/10 females receiving 200 mg/kg *N*-methylolacrylamide but not in mice given lower doses. Thymic lymphocytic necrosis was seen in 2/10 males and 4/10 females given 200 mg/kg but not in mice receiving lower doses. Hemorrhage, necrosis, and mineralization of the zona reticularis of the adrenal gland were present in 3/10 female mice at the 200 mg/kg dose. With the 100 mg/kg dose, 10/10 female mice had cytoplasmic vacuolization of the adrenal cortex. Vacuolization was also observed at lower doses and in vehicle controls. The lesion decreased in severity and incidence with decreasing dose.

Dose Selection Rationale: Because of deaths at 200 mg/kg and the severity of the adrenal gland lesions at 100 mg/kg in females, doses selected for mice for the 2-year studies of *N*-methylolacrylamide were 25 and 50 mg/kg, administered in water by gavage 5 days per week. Neurobehavioral changes were seen at 25 mg/kg and higher, but no microscopic lesions were seen in tissues of the nervous system at any dose.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed mice were up to 25% greater than those of vehicle controls for females and up to 13% greater for males (Table 21 and Figure 5). No compound-related clinical signs were observed.

TABLE 21. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

Week on Study	Vehicle Control		25 mg/kg			50 mg/kg		
	Av. Wt. (grams)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. Weighed
MALE								
1	23.3	50	23.7	101.7	50	23.5	100.9	50
2	25.3	50	25.3	100.0	50	25.4	100.4	50
3	26.1	50	27.0	103.4	50	26.8	102.7	50
4	27.5	50	27.8	101.1	50	28.0	101.8	50
5	28.3	50	29.6	104.6	50	29.3	103.5	50
6	30.0	50	30.5	101.7	50	30.3	101.0	50
7	29.9	50	30.9	103.3	50	30.5	102.0	50
8	31.3	50	32.0	102.2	49	31.5	100.6	50
9	32.1	50	32.8	102.2	49	32.2	100.3	50
10	32.8	50	33.2	101.2	49	33.2	101.2	50
11	33.3	50	34.3	103.0	49	33.6	100.9	50
12	33.6	50	34.3	102.1	49	34.1	101.5	50
13	33.8	50	35.0	103.6	49	34.4	101.8	50
17	35.6	49	35.7	100.3	48	36.4	102.2	50
22	36.4	49	37.7	103.6	45	38.6	106.0	50
26	38.0	(a) 48	38.7	101.8	44	39.7	104.5	50
31	39.7	47	40.2	101.3	43	41.9	105.5	49
34	38.7	46	40.5	104.7	42	40.9	105.7	49
38	41.3	46	42.8	103.6	42	43.9	106.3	48
42	41.2	46	43.2	104.9	42	43.6	105.8	48
46	41.3	45	43.5	105.3	42	45.0	109.0	48
50	40.8	45	43.8	107.4	42	45.4	111.3	48
54	41.6	45	45.7	109.9	42	47.1	113.2	47
58	42.2	45	45.2	107.1	42	46.8	110.9	47
62	42.2	45	45.0	106.6	41	47.3	112.1	47
66	43.3	44	45.7	105.5	39	47.6	109.9	46
70	41.6	42	44.9	107.9	37	47.1	113.2	41
75	42.5	42	45.5	107.1	35	48.0	112.9	39
79	42.9	41	45.4	105.8	35	47.5	110.7	38
82	43.3	41	45.2	104.4	35	47.0	108.5	36
86	43.7	40	46.0	105.3	35	48.7	111.4	34
90	42.6	38	45.4	106.6	32	46.9	110.1	33
94	41.5	37	43.8	105.5	29	44.7	107.7	29
98	39.8	34	42.1	105.8	29	44.1	110.8	26
102	39.5	31	42.4	107.3	22	43.5	110.1	23
104	39.2	31	42.2	107.7	21	43.0	109.7	23
FEMALE								
1	18.2	50	18.1	99.5	50	17.6	96.7	50
2	19.9	50	19.7	99.0	50	19.9	100.0	50
3	19.5	50	20.4	104.6	50	20.2	103.6	50
4	21.4	50	21.7	101.4	50	22.0	102.8	50
5	22.4	50	22.4	100.0	50	22.9	102.2	50
6	23.2	50	23.2	100.0	50	23.7	102.2	50
7	23.7	50	23.5	99.2	50	23.8	100.4	50
8	23.7	50	24.2	102.1	50	24.2	102.1	50
9	24.6	50	24.8	100.8	50	24.9	101.2	50
10	25.0	50	24.7	98.8	50	25.3	101.2	50
11	24.8	50	25.0	100.8	50	25.4	102.4	50
12	25.4	50	25.8	101.6	50	26.1	102.8	50
13	25.6	50	25.8	100.8	50	26.1	102.0	50
17	26.7	50	26.4	98.9	50	27.2	101.9	50
22	27.7	50	27.9	100.7	50	29.0	104.7	50
26	29.0	50	29.6	102.1	50	31.1	107.2	50
31	30.1	50	32.2	107.0	50	33.4	111.0	50
34	30.5	50	31.4	103.0	50	33.1	108.5	50
38	33.0	50	35.3	107.0	50	36.8	111.5	50
42	33.6	50	36.8	109.5	50	38.2	113.7	50
46	34.2	50	37.6	109.9	50	39.6	115.8	50
50	34.9	50	38.3	109.7	50	40.8	116.9	50
54	36.1	50	40.3	111.6	49	43.3	119.9	50
58	36.4	49	42.0	115.4	49	45.2	124.2	50
62	37.8	49	44.1	116.7	48	47.4	125.4	50
66	40.4	49	46.7	115.6	48	49.2	121.8	50
70	39.9	49	47.5	119.0	48	49.0	122.8	50
75	40.2	49	48.6	120.9	48	49.9	124.1	50
79	41.1	49	49.2	119.7	48	48.5	118.0	48
82	42.7	48	50.2	117.6	47	49.4	115.7	47
86	44.5	48	53.4	120.0	45	52.1	117.1	45
90	43.8	48	51.9	118.5	44	50.8	116.0	45
94	44.1	48	53.0	120.2	44	51.5	116.8	41
98	44.6	46	52.5	117.7	41	50.6	113.5	37
102	44.9	43	53.1	118.3	36	48.4	107.8	36
104	44.1	42	51.7	117.2	35	47.5	107.7	36

(a) The number of animals weighed was lower than the number of animals surviving.

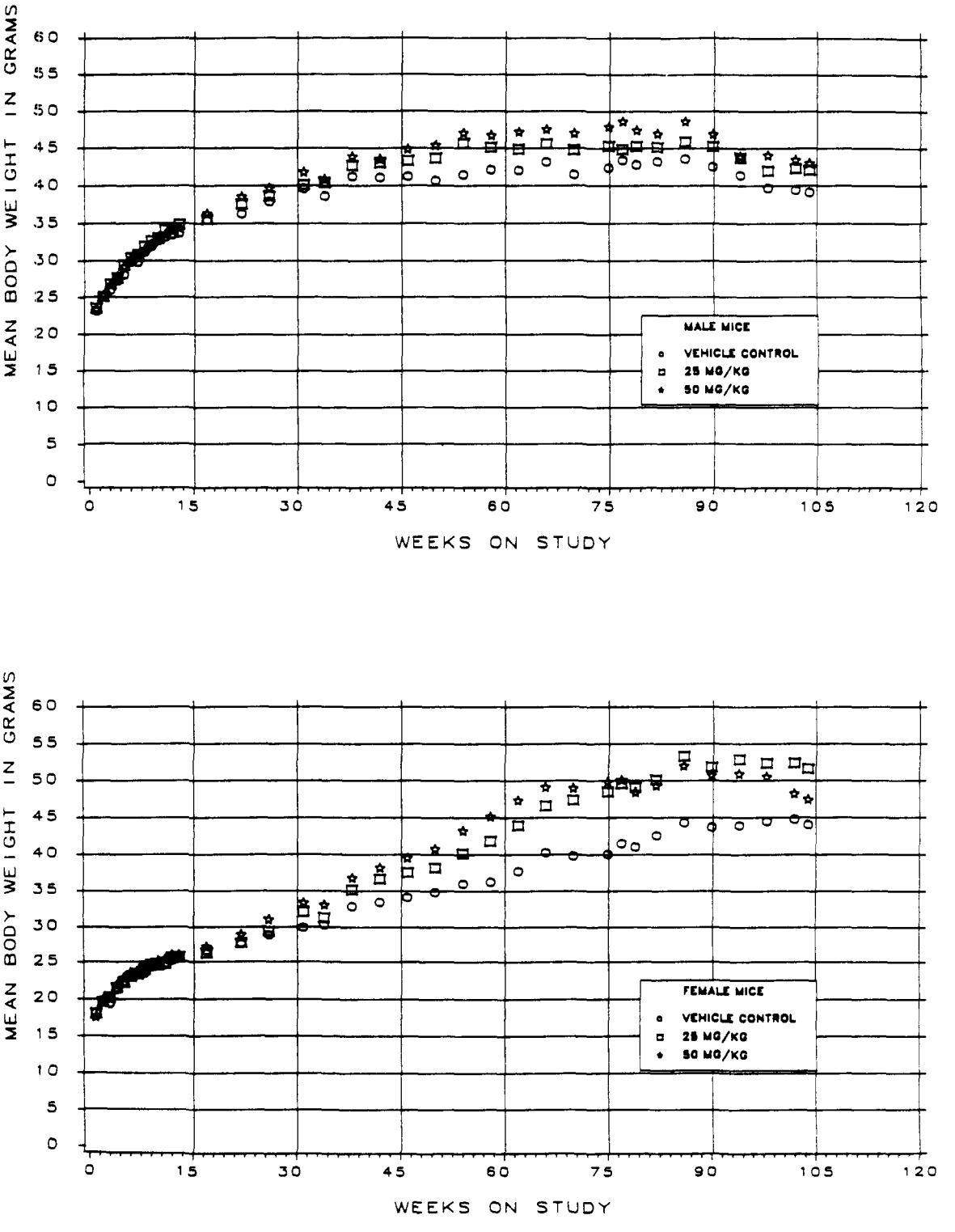


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED *N*-METHYLOLACRYLAMIDE IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered *N*-methylolacrylamide at the doses used in these studies and for vehicle controls are shown in Table 22 and in the Kaplan and Meier curves in Figure 6. Deaths of eight low dose male mice between week 8 and week 32 were considered to be due to a urinary infection; all other early deaths of low dose males and the majority of early deaths of high dose male mice were attributed to the presence of tumors. No significant differences in survival were observed between any groups of either sex.

TABLE 22. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	25 mg/kg	50 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	9	16	19
Moribund kills	12	14	11
Animals surviving until study termination	(b) 30	20	(b) 21
Survival P values (c)	0.125	0.070	0.128
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	5	9	10
Moribund kills	3	6	6
Accidentally killed	1	0	0
Animals missing	0	0	1
Animals surviving until study termination	41	35	33
Survival P values (c)	0.074	0.142	0.081

(a) First day of termination period: 731
(b) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

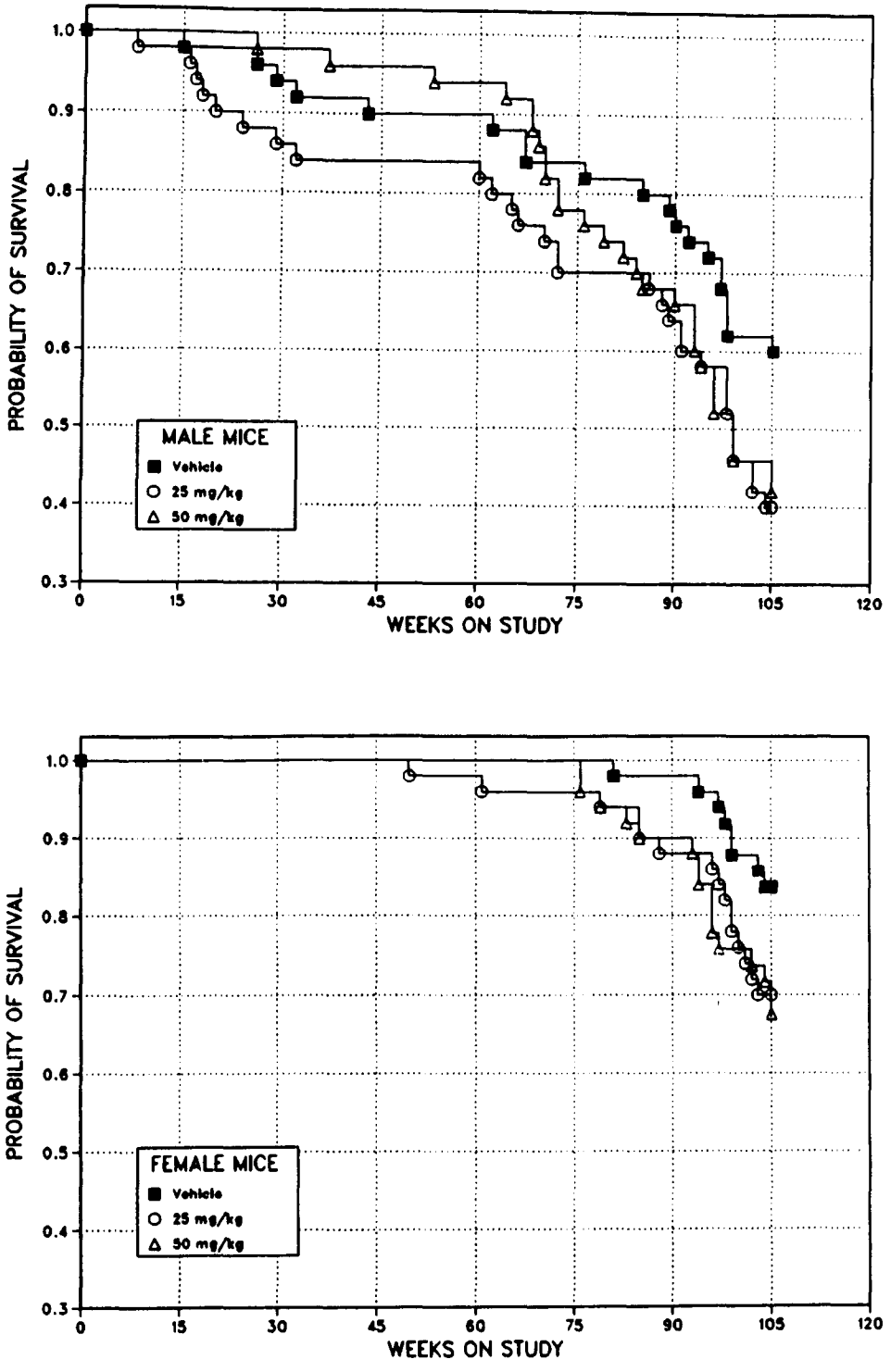


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED *N*-METHYLOLACRYLAMIDE IN WATER BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the Harderian gland, liver, lung, ovary, forestomach, spleen, kidney, and anterior pituitary gland.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

Harderian Gland: Incidences of adenomas of the Harderian gland were increased in male and female mice receiving *N*-methylolacrylamide (Table 23). Incidences of Harderian gland carcinomas were not significantly increased in dosed mice. Adenomas were well-demarcated masses that compressed the adjacent parenchyma and consisted of glandular structures composed of one or two layers of large, often tall, columnar epithelial cells with foamy cytoplasm. Frond-like projections of fibrovascular stroma covered by epithelial cells were present in glandular lumens. Carcinomas were distinguished from adenomas by the presence of greater cellular atypia, invasion, and metastasis. Some carcinomas contained solid sheets of pleomorphic epithelial cells, which often contained a large, clear intracytoplasmic vacuole.

Liver: Hepatocellular adenomas in male and female mice, hepatocellular carcinomas in males, and hepatocellular adenomas or carcinomas (combined) in males and females occurred with significant positive trends; the incidences of hepatocellular adenomas in high dose males and high dose females, hepatocellular carcinomas in dosed males, and hepatocellular adenomas or carcinomas (combined) in dosed males and high dose females were significantly greater than those in the vehicle controls (Table 24). Adenomas were well-demarcated lesions that compressed the adjacent parenchyma and consisted of closely packed hepatocyte cords with no associated central veins or portal areas and often no obvious sinusoids. The hepatocytes varied from smaller to larger than normal with slightly basophilic, eosinophilic, or vacuolated cytoplasm. Carcinomas were characterized by hepatocytes arranged in broad trabeculae that were four or more cells thick, or in solid sheets, or in a combination of both. Some carcinomas also metastasized.

TABLE 23. HARDERIAN GLAND LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

	Vehicle Control	25 mg/kg	50 mg/kg
MALE			
Hyperplasia			
Overall Rates	1/48 (2%)	0/49 (0%)	2/50 (4%)
Adenoma (b)			
Overall Rates	1/48 (2%)	14/49 (29%)	29/50 (58%)
Adjusted Rates	3.4%	54.8%	77.6%
Terminal Rates	1/29 (3%)	9/20 (45%)	13/21 (62%)
Day of First Observation	731	485	476
Life Table Tests	P<0.001	P<0.001	P<0.001
Logistic Regression Tests	P<0.001	P<0.001	P<0.001
Carcinoma			
Overall Rates	1/48 (2%)	0/49 (0%)	2/50 (4%)
Adenoma or Carcinoma (c)			
Overall Rates	2/48 (4%)	14/49 (29%)	30/50 (60%)
Adjusted Rates	6.9%	54.8%	80.4%
Terminal Rates	2/29 (7%)	9/20 (45%)	14/21 (67%)
Day of First Observation	731	485	476
Life Table Tests	P<0.001	P<0.001	P<0.001
Logistic Regression Tests	P<0.001	P<0.001	P<0.001
FEMALE			
Hyperplasia			
Overall Rates	1/47 (2%)	2/45 (4%)	1/48 (2%)
Adenoma (d)			
Overall Rates	5/47 (11%)	8/45 (18%)	20/48 (42%)
Adjusted Rates	12.5%	25.0%	49.1%
Terminal Rates	5/40 (13%)	8/32 (25%)	13/33 (39%)
Day of First Observation	731	731	589
Life Table Tests	P<0.001	P=0.146	P<0.001
Logistic Regression Tests	P<0.001	P=0.146	P<0.001
Carcinoma			
Overall Rates	0/47 (0%)	3/45 (7%)	2/48 (4%)
Adenoma or Carcinoma (e)			
Overall Rates	5/47 (11%)	11/45 (24%)	22/48 (46%)
Adjusted Rates	12.5%	33.1%	54.2%
Terminal Rates	5/40 (13%)	10/32 (31%)	15/33 (45%)
Day of First Observation	731	710	589
Life Table Tests	P<0.001	P=0.030	P<0.001
Logistic Regression Tests	P<0.001	P=0.031	P<0.001

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes).
(b) Historical incidence in water gavage vehicle controls (mean ± SD): 20/350 (6% ± 4%); historical incidence in untreated controls in NTP studies: 73/2,040 (4% ± 3%)
(c) Historical incidence in water gavage vehicle controls (mean ± SD): 22/350 (6% ± 4%); historical incidence in untreated controls in NTP studies: 79/2,040 (4% ± 3%)
(d) Historical incidence in water gavage vehicle controls (mean ± SD): 9/350 (3% ± 4%); historical incidence in untreated controls in NTP studies: 41/2,040 (2% ± 2%)
(e) Historical incidence in water gavage vehicle controls (mean ± SD): 12/350 (3% ± 4%); historical incidence in untreated controls in NTP studies: 48/2,040 (2% ± 2%)

TABLE 24. HEPATOCELLULAR TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	25 mg/kg	50 mg/kg
MALE			
Adenoma (a)			
Overall Rates	8/50 (16%)	4/50 (8%)	19/50 (38%)
Adjusted Rates	26.7%	18.5%	68.4%
Terminal Rates	8/30 (27%)	3/20 (15%)	13/21 (62%)
Day of First Observation	731	691	366
Life Table Tests	P<0.001	P=0.413N	P<0.001
Logistic Regression Tests	P=0.002	P=0.375N	P=0.004
Carcinoma (b)			
Overall Rates	6/50 (12%)	13/50 (26%)	12/50 (24%)
Adjusted Rates	19.4%	45.9%	38.3%
Terminal Rates	5/30 (17%)	6/20 (30%)	5/21 (24%)
Day of First Observation	729	455	502
Life Table Tests	P=0.027	P=0.012	P=0.031
Logistic Regression Tests	P=0.064	P=0.023	P=0.078
Adenoma or Carcinoma (c)			
Overall Rates	12/50 (24%)	17/50 (34%)	26/50 (52%)
Adjusted Rates	38.7%	59.3%	76.8%
Terminal Rates	11/30 (37%)	9/20 (45%)	14/21 (67%)
Day of First Observation	729	455	366
Life Table Tests	P<0.001	P=0.023	P<0.001
Logistic Regression Tests	P<0.001	P=0.055	P=0.001
FEMALE			
Adenoma (d)			
Overall Rates	3/50 (6%)	4/50 (8%)	17/49 (35%)
Adjusted Rates	7.3%	10.4%	48.2%
Terminal Rates	3/41 (7%)	2/35 (6%)	15/33 (45%)
Day of First Observation	731	616	653
Life Table Tests	P<0.001	P=0.423	P<0.001
Logistic Regression Tests	P<0.001	P=0.487	P<0.001
Carcinoma (e)			
Overall Rates	3/50 (6%)	3/50 (6%)	2/49 (4%)
Adenoma or Carcinoma (f)			
Overall Rates	6/50 (12%)	7/50 (14%)	17/49 (35%)
Adjusted Rates	13.7%	18.5%	48.2%
Terminal Rates	4/41 (10%)	5/35 (14%)	15/33 (45%)
Day of First Observation	675	616	653
Life Table Tests	P=0.001	P=0.392	P=0.002
Logistic Regression Tests	P=0.002	P=0.472	P=0.003

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 54/347 (16% ± 4%); historical incidence in untreated controls in NTP studies: 259/2,032 (13% ± 7%)
(b) Historical incidence in water gavage vehicle controls (mean ± SD): 56/347 (16% ± 8%); historical incidence in untreated controls in NTP studies: 379/2,032 (19% ± 7%)
(c) Historical incidence in water gavage vehicle controls (mean ± SD): 106/347 (31% ± 6%); historical incidence in untreated controls in NTP studies: 609/2,032 (30% ± 8%)
(d) Historical incidence in water gavage vehicle controls (mean ± SD): 22/348 (6% ± 5%); historical incidence in untreated controls in NTP studies: 107/2,032 (5% ± 4%)
(e) Historical incidence in water gavage vehicle controls (mean ± SD): 9/348 (3% ± 2%); historical incidence in untreated controls in NTP studies: 81/2,032 (4% ± 2%)
(f) Historical incidence in water gavage vehicle controls (mean ± SD): 29/348 (8% ± 5%); historical incidence in untreated controls in NTP studies: 184/2,032 (9% ± 5%)

Lung: Incidences of alveolar/bronchiolar adenomas and carcinomas were increased in high dose male mice, and the neoplasms occurred with significant positive trends (Table 25). The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) also occurred with a positive trend in female mice. Adenomas were well-demarcated masses that compressed the adjacent lung parenchyma and consisted of irregular alveolar or tubular structures lined by a single layer or cuboidal to columnar epithelial cells with a moderate amount of cytoplasm and hyperchromatic nuclei. Carcinomas often were less well demarcated than adenomas and sometimes demonstrated local invasion or metastasis. Neoplastic epithelial cells in carcinomas often were pleomorphic with large nuclei and scant cytoplasm and tended to grow in multiple layers or form solid areas.

Chronic inflammation and alveolar epithelial hyperplasia were observed at slightly increased incidences in dosed mice (chronic inflammation--male: vehicle control, 8/49; low dose, 12/50; high dose, 20/50; female: 12/50; 28/50; 14/49; alveolar epithelial hyperplasia--male: 10/49; 17/50; 19/50; female: 8/50; 26/50; 17/49). These two lesions generally occurred together and appeared to be part of the same lesion. The lesions consisted of clusters of alveoli adjacent to bronchioles that were lined by flattened to cuboidal to columnar cells, many of which were ciliated, and were filled with mucus mixed with inflammatory cells. The lesions were similar in appearance to chronic lesions of Sendai virus infection. Seven of 10 sentinel mice were found to be seropositive for Sendai virus at 18 months.

Ovary: Atrophy was observed at increased incidences in female mice given *N*-methylolacrylamide (vehicle control, 3/50; low dose, 39/45; high dose, 38/47). Atrophy was characterized by a complete absence of follicular and luteal activity, often accompanied by a decrease in ovarian size. Benign granulosa cell tumors occurred at significantly greater incidences in dosed female mice than in vehicle controls (Table 26). The neoplasms were discrete masses that had replaced some or all of the affected ovary and were composed of cells that resembled normal ovarian granulosa cells and formed follicular, tubular, solid, or adenomatous structures.

Forestomach: Squamous papillomas occurred in the forestomach of a few male and female mice that received *N*-methylolacrylamide (male: vehicle control, 0/50; low dose, 1/49; high dose, 2/48; female: 0/46; 0/6; 2/44). The highest observed incidence of forestomach neoplasms in water gavage vehicle control $B6C3F_1$ mice is 3/50 for males and 2/49 for females.

Spleen: Hematopoietic cell proliferation was observed at increased incidences in high dose mice (male: vehicle control, 11/50; low dose, 13/26; high dose, 38/50; female: 15/50; 10/19; 40/48). The proliferation was considered a secondary response to neoplastic and inflammatory lesions in various organs.

Kidney: Chronic nephropathy was observed at increased incidences in high dose female mice (male: vehicle control, 21/50; low dose, 4/22; high dose, 22/50; female: 10/50; 3/11; 23/48). The nephropathy was generally of minimal to mild severity and was consistent with changes in the kidney of aging $B6C3F_1$ mice.

Anterior Pituitary Gland: The incidence of adenomas of the pars distalis in high dose female mice was significantly lower than that in vehicle controls (vehicle control, 13/49; low dose, 5/14; high dose, 4/43).

TABLE 25. ALVEOLAR/BRONCHIOLAR TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	25 mg/kg	50 mg/kg
MALE			
Adenoma (a)			
Overall Rates	3/49 (6%)	6/50 (12%)	11/50 (22%)
Adjusted Rates	10.3%	21.6%	40.1%
Terminal Rates	3/29 (10%)	2/20 (10%)	6/21 (29%)
Day of First Observation	731	600	366
Life Table Tests	P=0.005	P=0.129	P=0.006
Logistic Regression Tests	P=0.010	P=0.184	P=0.015
Carcinoma (b)			
Overall Rates	2/49 (4%)	4/50 (8%)	10/50 (20%)
Adjusted Rates	6.3%	18.3%	34.6%
Terminal Rates	1/29 (3%)	3/20 (15%)	4/21 (19%)
Day of First Observation	675	687	589
Life Table Tests	P=0.003	P=0.213	P=0.006
Logistic Regression Tests	P=0.005	P=0.253	P=0.011
Adenoma or Carcinoma (c)			
Overall Rates	5/49 (10%)	10/50 (20%)	18/50 (36%)
Adjusted Rates	16.3%	37.2%	58.2%
Terminal Rates	4/29 (14%)	5/20 (25%)	9/21 (43%)
Day of First Observation	675	600	366
Life Table Tests	P<0.001	P=0.045	P<0.001
Logistic Regression Tests	P<0.001	P=0.073	P=0.001
FEMALE			
Adenoma (d)			
Overall Rates	4/50 (8%)	4/50 (8%)	7/49 (14%)
Carcinoma (e)			
Overall Rates	2/50 (4%)	5/50 (10%)	7/49 (14%)
Adjusted Rates	4.9%	13.2%	19.2%
Terminal Rates	2/41 (5%)	4/35 (11%)	5/33 (15%)
Day of First Observation	731	421	580
Life Table Tests	P=0.034	P=0.167	P=0.045
Logistic Regression Tests	P=0.061	P=0.243	P=0.076
Adenoma or Carcinoma (f)			
Overall Rates	6/50 (12%)	8/50 (16%)	13/49 (27%)
Adjusted Rates	14.6%	20.6%	33.8%
Terminal Rates	6/41 (15%)	5/35 (14%)	9/33 (27%)
Day of First Observation	731	421	580
Life Table Tests	P=0.019	P=0.284	P=0.025
Logistic Regression Tests	P=0.042	P=0.387	P=0.057

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 46/347 (13% ± 8%); historical incidence in untreated controls in NTP studies: 255/2,034 (13% ± 6%)
(b) Historical incidence in water gavage vehicle controls (mean ± SD): 22/347 (6% ± 5%); historical incidence in untreated controls in NTP studies: 102/2,034 (5% ± 3%)
(c) Historical incidence in water gavage vehicle controls (mean ± SD): 65/347 (19% ± 8%); historical incidence in untreated controls in NTP studies: 348/2,034 (17% ± 7%)
(d) Historical incidence in water gavage vehicle controls (mean ± SD): 25/349 (7% ± 3%); historical incidence in untreated controls in NTP studies: 101/2,026 (5% ± 4%)
(e) Historical incidence in water gavage vehicle controls (mean ± SD): 8/349 (2% ± 2%); historical incidence in untreated controls in NTP studies: 45/2,026 (2% ± 2%)
(f) Historical incidence in water gavage vehicle controls (mean ± SD): 33/349 (9% ± 4%); historical incidence in untreated controls in NTP studies: 145/2,026 (7% ± 4%)

TABLE 26. BENIGN OVARIAN GRANULOSA CELL TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Overall Rates	0/50 (0%)	5/45 (11%)	5/47 (11%)
Adjusted Rates	0.0%	16.1%	15.6%
Terminal Rates	0/41 (0%)	5/31 (16%)	5/32 (16%)
Day of First Observation		731	731
Life Table Tests	P=0.017	P=0.015	P=0.016
Logistic Regression Tests	P=0.017	P=0.015	P=0.016

(a) Historical incidence of luteomas or granulosa cell tumors (combined) in water gavage vehicle controls (mean ± SD): 2/339 (0.6% ± 1.0%); historical incidence in untreated controls in NTP studies: 13/1,867 (0.7% ± 2%)

N-Methylolacrylamide was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 when tested with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 at doses up to 10 mg/plate (Table 27; Zeiger et al., 1988). When tested for cytogenetic effects in cultured Chinese hamster ovary cells, *N*-methylolacrylamide induced dose-related increases in both sister chromatid exchanges (SCEs) and chromosomal aberrations with and without Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables 28 and 29). Cells receiving the highest doses in the SCE trials without S9 required delayed harvest to offset chemical-induced cell cycle delay, as did all the cell cultures in the chromosomal aberration test. Results from a short-term in vivo mouse bone marrow micronucleus test with *N*-methylolacrylamide dissolved in corn oil were negative; doses up to 150 mg/kg (administered twice by intraperitoneal injection at 24-hour intervals) did not cause an increase in micronucleated polychromatic erythrocytes (Table 30).

TABLE 27. MUTAGENICITY OF *N*-METHYLOLACRYLAMIDE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	10%	30%	10%	30%
TA100							
	0	134 ± 8.2	120 ± 14.3	140 ± 7.2	140 ± 3.5	139 ± 5.2	111 ± 11.5
	100	129 ± 3.2	141 ± 0.7	129 ± 11.0	140 ± 9.6	133 ± 14.4	132 ± 17.6
	333	133 ± 8.2	107 ± 4.7	153 ± 9.4	115 ± 6.4	143 ± 7.7	141 ± 4.9
	1,000	144 ± 4.8	99 ± 14.6	138 ± 8.0	145 ± 6.8	145 ± 9.3	140 ± 9.3
	3,333	143 ± 3.9	120 ± 6.1	134 ± 11.6	141 ± 5.2	133 ± 3.5	129 ± 3.4
	10,000	147 ± 2.7	83 ± 9.2	162 ± 3.5	151 ± 15.8	138 ± 11.2	152 ± 6.4
	Trial summary	Negative	Negative	Negative	Negative	Negative	Equivocal
	Positive control (c)	791 ± 116.5	455 ± 9.3	2,033 ± 59.0	459 ± 27.0	508 ± 21.6	338 ± 13.3
TA1535							
	0	19 ± 1.9	17 ± 2.9	10 ± 0.7	11 ± 0.6	9 ± 1.2	7 ± 0.6
	100	19 ± 1.3	19 ± 5.2	10 ± 0.7	7 ± 1.2	9 ± 0.3	15 ± 2.6
	333	18 ± 1.0	20 ± 4.4	11 ± 2.3	10 ± 0.3	8 ± 1.8	12 ± 1.9
	1,000	18 ± 3.5	14 ± 2.3	8 ± 0.9	10 ± 0.6	11 ± 2.0	12 ± 2.3
	3,333	19 ± 0.7	15 ± 4.9	8 ± 2.1	13 ± 2.4	10 ± 1.7	10 ± 1.0
	10,000	9 ± 0.9	9 ± 5.5	8 ± 0.3	14 ± 6.0	9 ± 1.2	11 ± 0.9
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	519 ± 13.4	391 ± 27.1	403 ± 46.4	383 ± 25.1	195 ± 0.6	189 ± 10.5
TA97							
	0	100 ± 4.3	147 ± 8.7	112 ± 1.2	133 ± 10.1	181 ± 4.5	142 ± 3.0	197 ± 4.0
	33		155 ± 9.0		139 ± 11.6	173 ± 15.6		
	100	90 ± 5.1	151 ± 4.3	97 ± 6.6	146 ± 4.9	169 ± 10.7	155 ± 20.3	200 ± 3.2
	333	84 ± 4.2	157 ± 4.6	96 ± 2.6	143 ± 4.1	163 ± 4.7	153 ± 4.4	196 ± 3.5
	1,000	81 ± 6.6	164 ± 14.0	95 ± 1.2	145 ± 3.0	182 ± 6.7	155 ± 12.3	195 ± 3.1
	3,333	70 ± 3.9	157 ± 6.7	90 ± 7.5	159 ± 8.8	186 ± 5.9	164 ± 5.9	194 ± 4.4
	10,000	1 ± 0.9		36 ± 16.9			158 ± 17.6	196 ± 2.1
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,717 ± 106.6	901 ± 40.4	1,771 ± 39.6	1,682 ± 19.4	1,011 ± 61.6	959 ± 48.4	596 ± 12.7
TA98							
	0	15 ± 0.3	17 ± 1.8	32 ± 2.0	29 ± 2.9	25 ± 1.7	18 ± 2.7
	100	17 ± 0.3	24 ± 2.9	28 ± 2.3	34 ± 1.2	29 ± 2.6	21 ± 3.1
	333	18 ± 1.5	16 ± 2.3	31 ± 4.1	29 ± 1.2	29 ± 0.9	25 ± 0.3
	1,000	13 ± 1.5	22 ± 6.2	29 ± 0.0	39 ± 1.5	23 ± 2.1	20 ± 2.7
	3,333	19 ± 3.1	14 ± 3.8	28 ± 6.8	30 ± 6.4	24 ± 1.9	22 ± 4.8
	10,000	12 ± 2.9	8 ± 0.5	24 ± 7.5	32 ± 1.2	22 ± 1.3	23 ± 9.5
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,731 ± 50.2	1,894 ± 105.9	1,218 ± 172.0	236 ± 18.5	254 ± 25.5	157 ± 6.6

(a) Study performed at SRI International. The detailed protocol is presented by Haworth et al. (1983), and the data, with protocol modifications, are included in Zeiger et al. (1988). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA97.

TABLE 28. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *N*-METHYLOLACRYLAMIDE (a)

	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,045	457	0.44	9.1	25.8	
N-Methylolacrylamide	16.7	50	1,045	520	0.50	10.4	25.8	114.3
	50	50	1,046	524	0.50	10.5	25.8	115.4
	166.7	50	1,043	589	0.56	11.8	(d) 30.8	129.7
Mitomycin C	0.001	50	1,051	569	0.54	11.4	25.8	125.3
	0.01	5	105	197	1.88	39.4	25.8	433.0
Trial 2--Summary: Positive								
Dimethyl sulfoxide		25	525	276	0.53	11.0	25.8	
N-Methylolacrylamide	125	25	525	283	0.54	11.3	25.8	102.7
	166.7	25	525	372	0.71	14.9	25.8	135.5
	250	25	525	405	0.77	16.2	(d) 33.0	147.3
Mitomycin C	0.001	25	525	327	0.62	13.1	25.8	119.1
	0.01	5	105	214	2.04	42.8	25.8	389.1
+S9 (e)--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,050	377	0.36	7.5	25.8	
N-Methylolacrylamide	166.7	50	1,050	407	0.39	8.1	25.8	108.0
	500	50	1,049	436	0.42	8.7	25.8	116.0
	1,700	50	1,043	565	0.54	11.3	25.8	150.7
Cyclophosphamide	0.4	50	1,049	586	0.56	11.7	25.8	156.0
	2	5	103	181	1.76	36.2	25.8	482.7

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) and (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE 29. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY *N*-METHYLOLACRYLAMIDE (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time: 20.2 h (d)					Harvest time: 20.2 h (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	200	2	0.01	0.5		200	3	0.02	0.5
N-Methylolacrylamide					*N*-Methylolacrylamide				
250	200	16	0.08	7.0	2,500	200	95	0.48	11.5
375	200	48	0.24	18.5	3,750	25	95	3.80	56.0
500	50	57	1.14	52.0	5,000	25	149	5.96	92.0
Summary: Positive					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.05	200	67	0.34	24.0	6.25	200	34	0.17	14.0
0.08	25	15	0.60	40.0	12.5	25	42	1.68	72.0
Trial 2--Harvest time: 20.2 hours (d)									
Dimethyl sulfoxide									
	100	0	0.00	0.0					
N-Methylolacrylamide									
375	100	42	0.42	26.0					
437.5	50	53	1.06	64.0					
500	50	79	1.58	66.0					
Summary: Positive									
Mitomycin C									
0.05	100	20	0.20	19.0					
0.08	25	29	1.16	40.0					

(a) Study performed at Litton Bionetics, Inc.; Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.

TABLE 30. INCIDENCE OF MICRONUCLEI IN BONE MARROW POLYCHROMATIC ERYTHROCYTES OF MALE B6C3F$_1$ MICE EXPOSED TO *N*-METHYOLACRYLAMIDE (a)

Dose (mg/kg per injection)	Micronucleated PCE/ 2,000 Cells (b)	Number of Animals
Corn oil (c)	3.0 ± 0.9	5
N-methylolacryamide		
37.5	3.0 ± 0.6	5
75	1.4 ± 0.4	5
150	1.6 ± 0.6	5
Dimethylbenzanthracene (d)		
100	73.6 ± 20.7	5

(a) Study performed at Environmental Health Research and Testing, Inc. PCEs = polychromatic erythrocytes. Male mice were given two intraperitoneal injections (at 24-h intervals) of *N*-methylolacrylamide dissolved in corn oil. Bone marrow smears were prepared 24 h after the second injection; 2,000 PCEs were scored for the incidence of micronuclei in each of five animals per dose group.
(b) Mean ± standard error of the mean of the pooled results from all animals scored within a dose group. Results were negative ($P>0.1$).
(c) Solvent control animals received 0.4 ml corn oil per injection.
(d) Positive control

IV. DISCUSSION AND CONCLUSIONS

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N-Methylolacrylamide was evaluated for toxicity and carcinogenicity in 16-day, 13-week, and 2-year studies. The chemical was administered by gavage in water to F344 rats and $B6C3F_1$ mice of each sex. *N*-Methylolacrylamide was studied because of its widespread use in textiles, paints, and other products. Results of recent long-term carcinogenicity studies of acrylamide in rodents were positive (IARC, 1986), suggesting that *N*-methylolacrylamide also might be a carcinogen.

N-Methylolacrylamide, like acrylamide, is clearly clastogenic to mammalian cells in vitro. Although it does not induce gene mutations in bacteria, it has been shown to induce chromosomal aberrations in cultured Chinese hamster ovary cells in both the absence and presence of S9. However, the one in vivo test for which results are available showed no induction of micronuclei in the bone marrow polychromatic erythrocytes of mice injected intraperitoneally with the chemical. Acrylamide, on the other hand, in addition to inducing chromosomal aberrations in vitro, has also been shown to be clastogenic in vivo. It induces chromosomal aberrations and micronuclei in mouse bone marrow cells and dominant lethal mutations and inherited translocations in mouse germ cells.

Acrylamide may exert its mutagenic effects through interaction with proteins and microtubules, as well as with DNA. Based on aneuploidy and polyploidy observed in mouse bone marrow and spermatagonial cells, Shiraishi (1978) speculated that acrylamide may disrupt cytoplasmic microtubules. In studies with [^{14}C]acrylamide, Sega et al. (1988) found that the chromosome breakage and dominant lethal effects reported for acrylamide in mouse germ cells correlated with the levels of protamine alkylation but not those of DNA alkylation and speculated that stress on the chromosome structure caused by protamine alkylation might be the mechanism for acrylamide's chromosome-damaging effects.

Acrylamide and related compounds have also been recognized as neurotoxins and are considered good examples of compounds that show cumulative toxicity. Clinical signs of neurologic effects were seen in the 16-day studies of *N*-methylolacrylamide at doses of 100-400 mg/kg in rats and 200 and 400 mg/kg in mice. At the highest dose, rats appeared to have increased motor activity and exaggerated startle responses, but most animals died before developing ataxia or other signs of peripheral neuropathy, signs that were seen later at lower doses. Weight gains were dose related in rats but were difficult to interpret in mice because of poor weight gain in vehicle control males and nonuniformity of starting weights in females. Neurotoxicity was a possible cause of death in these studies, although no major neural lesions were observed histopathologically. A number of microscopic changes, including dysplasia of the nasal and tracheal epithelium, hyperplasia of the tracheal and bronchiolar epithelium, and hepatocellular necrosis, were noted in various organs of dosed animals. Certain changes, including vacuolar degeneration of the myocardial fibers and sinusoidal congestion of the liver, were observed only in mice that died early.

In the 13-week studies, all rats and mice that received 200 mg/kg died during the first 5 weeks, and most of the rats that received 100 mg/kg died during weeks 5-8. Neurotoxic effects were evident; the time of onset of hind limb ataxia and progression to hind limb paralysis was related to the cumulative dose of *N*-methylolacrylamide. A battery of neurobehavioral assessments was performed on both rats and mice during weeks 6 and 13. Measures of forelimb and hind limb grip strength showed dose-related deficits in male and female rats and mice at both testing periods and increased landing foot spread in rats. Mice were tested in the rotarod performance assay. Results showed a rather inconsistent pattern of poorer performance by dosed animals. Motor activity did not appear to be affected consistently in dosed rats or mice, but startle response appeared decreased in dosed rats. These results suggest the presence of peripheral neuropathy in both rats and mice administered *N*-methylolacrylamide. Peripheral nerve lesions were seen in rats, primarily various degenerative lesions in the myelin; degeneration and cellular necrosis also were noted in the granular cell layer of the cerebellum in rats, along with axon filament and myelin sheath degeneration of the brain stem and spinal cord. However, no neural lesions were evident

microscopically in mice. Peripheral nerve lesions were detected in rats at doses as low as 25 mg/kg. This was accomplished with special histopathologic procedures outlined in the Materials and Methods section. These procedures were not used on the mice. However, brain stem and spinal cord lesions were also noted in rats at 50 mg/kg and higher by the traditional histopathologic methods. These lesions were not seen in mice at doses as high as 200 mg/kg in the 13-week studies. Increased sensitivity to the neurotoxic effects of *N*-methylolacrylamide for rats compared with those for mice also was suggested by a variety of urinary bladder lesions in rats, which included hemorrhage and inflammation, hyperplasia, and edema of the mucosal cells. These lesions resulted from urinary bladder distension that was probably secondary to deficits in the neural control of urination.

Doses for the 2-year studies in rats were set at 0, 6, and 12 mg/kg per day for both males and females because 12 mg/kg was the highest dose at which no evidence of histopathologic or neurobehavioral effects was seen in the 13-week studies. The severity of the neural lesions at 25 mg/kg was not believed to be life threatening, but the recognized cumulative nature of the neurotoxic effects of this and other acrylamide-like compounds and the degree of neurobehavioral effects in the 13-week studies with 25 mg/kg indicated selection of a lower dose.

Lesions used as the basis for dose selection for mice in the 2-year studies were different from those used for rats. Although neurobehavioral effects were seen at doses down to 25 mg/kg, neuropathologic effects were not seen microscopically. All mice given 200 mg/kg died by week 5, and necrosis of hepatocytes, thymic lymphocytes, and adrenal cells of the zona reticularis was seen in these animals. A separate adrenal cortical lesion, cytoplasmic vacuolization, was seen at lower doses and appeared dose related in severity. The significance of this lesion during a 2-year study could not be predicted, and a high dose of 50 mg/kg was chosen for the 2-year studies, based on the mild-to-moderate severity of the lesion at this dose.

In the 2-year studies in rats, body weights of high dose males and females were similar to those of vehicle controls, and survival also was similar, except for low dose females. Seven low dose females died during weeks 61-77, compared with one each in the vehicle control and high dose groups. After this period, the number of deaths was similar in all groups. Six of the seven low dose females dying during weeks 61-77 had neoplastic lesions. Two had uterine stromal sarcomas, two had mammary gland fibroadenomas, one had mononuclear cell leukemia, and one had a clitoral gland adenoma. This cluster of somewhat early neoplasms is unusual but is not attributable to *N*-methylolacrylamide administration.

There were no clinical observations in the 2-year studies that would suggest the development of peripheral neuropathy, but specific neurobehavioral assessments were not performed. Nonetheless, the lack of clinical signs suggests that the doses used in these studies were sufficiently low to prevent cumulative neurotoxic effects. No biologically significant increases in neoplastic or nonneoplastic lesions in rats were attributed to the administration of *N*-methylolacrylamide. Cystic degeneration of the liver was increased slightly in high dose male rats. Administration of somewhat higher doses to rats might have provided a more rigorous assessment of the carcinogenic potential of *N*-methylolacrylamide, but a top dose of no more than 20-25 mg/kg could have been used, based on the collected observations of the 13-week studies.

The *N*-methylolacrylamide rat study results contrast with the results of 2-year studies of acrylamide given in drinking water to F344 rats (Johnson et al., 1986). The doses in the Johnson studies ranged up to 2 mg/kg per day. No clinical signs of neuropathy were seen, but the number of deaths increased during the last 4 months of the studies in high dose males and females. In females, increased tumor incidences were observed in the mammary gland, central nervous system, thyroid gland, follicular epithelium, oral tissues, uterus (adenocarcinomas unrelated to stromal sarcomas), and clitoral gland. In males, the incidences of thyroid gland follicular cell tumors and scrotal mesotheliomas were increased. No evidence has been obtained which would suggest significant metabolism of *N*-methylolacrylamide to acrylamide in vivo (Edwards, 1974).

IV. DISCUSSION AND CONCLUSIONS

The results of the 2-year studies of *N*-methylolacrylamide in mice differed sharply from the results of the studies in rats. In mice, no significant clinical signs or obvious neurotoxic effects were observed, but body weights were substantially higher in the dosed animals than in the vehicle controls. The body weight patterns of vehicle controls did not differ from those normally observed in 2-year studies, and those of dosed mice were towards the high end of the vehicle control range. The reasons for this finding are not entirely clear, although subclinical toxic effects on the nervous system, and perhaps on the neuroendocrine system, may have reduced the general level of activity of the animals receiving the chemical.

Survival of dosed male and female mice was somewhat lower than that seen in vehicle controls, primarily because of an increase in neoplastic lesions. In addition, eight low dose male mice with urinary tract infections died early during the first year. These infections are common in situations of urine retention, but it is not clear why high dose males did not also die more frequently from similar infections if this was involved. Fighting among the group-housed male mice may have contributed to the infections.

Substantially increased incidences of tumors of the Harderian gland, liver, lung, and ovary were observed in mice administered *N*-methylolacrylamide for 2 years. The incidences of Harderian gland adenomas in high dose mice (male, 58%; female, 42%) were far in excess of the vehicle control incidences (male, 2%; female, 11%) or the historical control incidences (male, 4%; female, 2%; Tables C4a and D4a). The incidences of hyperplasia and carcinomas were not increased in dosed mice compared with those in vehicle controls. Harderian gland neoplasms have been described in a number of strains of mice (Sheldon et al., 1983). The majority of adenocarcinomas observed among these spontaneous tumors appeared to arise from adenomas, suggesting the progression of benign to malignant neoplasms in this organ.

The incidences of alveolar/bronchiolar neoplasms of the lung were increased in dosed male and female mice. The vehicle control incidences for the neoplasms in these studies were close to the expected values (Tables C4c and D4c). The incidences of both adenomas and carcinomas were increased in dosed male mice; in females, the increased incidences of carcinomas and the combined tumors were statistically significant. Alveolar/bronchiolar adenomas and carcinomas are generally similar in morphologic appearance; the distinction between them often is based primarily on size. Adenomas are smaller than carcinomas, and growth of these tumors is usually accompanied by an increase in cellular anaplasia and foci of malignant cells (Ward et al., 1979).

The serology assessments and certain of the lung lesions in mice indicated that a Sendai infection had occurred during the studies. Although it appears unlikely that the Sendai infection alone could have influenced the lung tumor incidence (Rao et al., 1989), an interaction between the viral effects and effects of *N*-methylolacryamide administration, possibly affecting the lung tumor response, cannot be ruled out.

Ovarian atrophy was increased in dosed female mice. This lesion was characterized by an increase in interstitial cells and an accumulation of phagocytes that contained pigment. Increased numbers and hypertrophy of interstitial cells occurred with increased follicular atresia. Benign granulosa cell tumors of the ovary were observed in five low dose and five high dose female mice. The incidences in dosed animals are markedly greater than those in concurrent or historical vehicle controls (approximately 0.6%; Table D4d). Although seen infrequently, granulosa cell tumors (benign and malignant) are the most commonly observed ovarian tumors in control $B6C3F_1$ mice (Alison and Morgan, 1987). Evidence has been presented suggesting a relationship between follicular atrophy and the development of ovarian neoplasia (Maronpot, 1987). This theory proposes that oocyte destruction and the subsequent decrease in estrogen production lead to a compensatory increase in pituitary gonadotropin release. The increased stimulation by gonadotropins stimulates cell proliferation in the ovary which, in some manner, promotes the eventual development of neoplasia. On the surface, the observation of ovarian atrophy in 87% of low dose mice and 81% of high dose mice and the occurrence of five tumors in the low

dose groups and five in the high dose groups appear consistent with such a hypothesis. If this theory is correct, the reason that a higher incidence of tumors was not seen is not clear. Nonetheless, in these studies, serum hormone levels were not measured, and the applicability of the proposed mechanism to the neoplasms observed is not known.

Hepatocellular adenomas were increased in high dose male and female mice, and hepatocellular carcinomas were increased in dosed male mice. The incidences of these neoplasms in the vehicle control groups of males and females were similar to those normally seen in 2-year studies (see Table 24), and the incidences of adenomas or carcinomas (combined) in high dose males and females exceeded the highest observed vehicle control incidences for water gavage studies (Tables C4b and D4b), although higher incidences have been observed in untreated control male mice. No increase in metastases was observed in dosed mice.

A number of factors have been shown to influence the occurrence of liver neoplasms in mice (Maronpot et al., 1987). Castration decreases the spontaneous and carcinogen-induced incidence in males, and ovariectomy increases the incidence in females. As noted above, ovarian atrophy was observed in dosed female mice. Decreased body weight is thought to lead to a lower incidence of liver neoplasms in male mice (Rao et al., 1987). In the current study, the dosed male mice were 10%-13% heavier than vehicle controls during the peak weight period in the study. Increased cell turnover in the liver has been associated with increased incidences of liver neoplasms (Maronpot et al., 1987). No increase in liver weight was seen in males or females in the 13-week studies at the doses used in the 2-year studies, and although hepatocellular necrosis was observed at the top dose (200 mg/kg), none was observed at lower doses in the 13-week studies.

The mouse liver has been shown to be sensitive to the development of neoplasms after administration of both genotoxic and nongenotoxic chemicals (Ashby and Tennant, 1988). Most of the factors described above that affect the incidence of liver neoplasms in mice are presumed to work through nongenotoxic mechanisms. The increases in liver neoplasms in the current studies may reflect the effects of a combination of factors. *N*-Methylolacrylamide is genotoxic, and the ultimate liver tumor response may have been influenced by the ovarian atrophy in females and the increased weight gain in dosed males.

The experimental and tabulated data for the NTP Technical Report on *N*-methylolacrylamide were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Under the conditions of these 2-year studies, there was *no evidence of carcinogenic activity** of *N*-methylolacrylamide for male or female F344/N rats receiving doses of 6 or 12 mg/kg per day by aqueous gavage. There was *clear evidence of carcinogenic activity* of *N*-methylolacrylamide for male B6C3F$_1$ mice, based on increased incidences of neoplasms of the Harderian gland, liver, and lung. There was *clear evidence of carcinogenic activity* of *N*-methylolacrylamide for female B6C3F$_1$ mice, based on increased incidences of neoplasms of the Harderian gland, liver, lung, and ovary.

In rats, because no biologically important toxic effects were attributed to *N*-methylolacrylamide administration, somewhat higher doses could have been used to increase the sensitivity of these studies for determining the presence or absence of a carcinogenic response. In female mice, ovarian atrophy was compound related.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

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V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, colon	(49)	*(50)	(50)
Mesothelioma malignant		1 (2%)	
Intestine large, rectum	(49)	*(50)	(49)
Mesothelioma malignant		1 (2%)	
Intestine small, ileum	(48)	*(50)	(50)
Mesothelioma malignant		1 (2%)	
Intestine small, jejunum	(49)	*(50)	(50)
Mesothelioma malignant		1 (2%)	
Liver	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)	
Histiocytic sarcoma	1 (2%)		
Leukemia mononuclear	17 (34%)	18 (36%)	24 (48%)
Neoplastic nodule	4 (8%)	1 (2%)	
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear	2 (4%)		
Lipoma			1 (2%)
Mesothelioma malignant		1 (2%)	
Pancreas	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	
Mesothelioma malignant		1 (2%)	
Salivary glands	(50)	*(50)	(49)
Leukemia mononuclear	2 (4%)		
Stomach, forestomach	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Papilloma squamous	1 (2%)		
Stomach, glandular	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Tongue	*(50)	*(50)	*(50)
Papilloma squamous			1 (2%)
Tooth	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	6 (12%)		9 (18%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma		2 (4%)	1 (2%)
Leukemia mononuclear	12 (24%)	7 (14%)	15 (30%)
Adrenal gland, medulla	(49)	(50)	(50)
Leukemia mononuclear	12 (24%)	7 (14%)	15 (30%)
Pheochromocytoma malignant	2 (4%)	2 (4%)	
Pheochromocytoma benign	10 (20%)	7 (14%)	11 (22%)
Bilateral, pheochromocytoma benign	8 (16%)		2 (4%)
Islets, pancreatic	(50)	*(50)	(50)
Adenoma			2 (4%)
Leukemia mononuclear	1 (2%)		
Parathyroid gland	(48)	*(50)	(45)
Adenoma	1 (2%)		
Pituitary gland	(50)	*(50)	(50)
Leukemia mononuclear	4 (8%)		3 (6%)
Pars distalis, adenoma	18 (36%)	14 (28%)	13 (26%)
Pars distalis, adenoma, multiple	1 (2%)		
Pars distalis, carcinoma			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(50)	*(50)	(50)
C-cell, adenoma	7 (14%)	4 (8%)	9 (18%)
C-cell, carcinoma	1 (2%)		1 (2%)
Follicular cell, carcinoma		1 (2%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	*(50)	(49)
Mesothelioma malignant		1 (2%)	1 (2%)
Preputial gland	(49)	*(50)	(48)
Adenoma	2 (4%)	2 (4%)	3 (6%)
Leukemia mononuclear	1 (2%)		
Squamous cell carcinoma		1 (2%)	
Prostate	(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)		
Testes	(50)	*(50)	(50)
Mesothelioma malignant	1 (2%)		2 (4%)
Bilateral, mesothelioma malignant		1 (2%)	
Bilateral, interstitial cell, adenoma	33 (66%)	33 (66%)	38 (76%)
Interstitial cell, adenoma	7 (14%)	8 (16%)	8 (16%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		2 (4%)
Bone marrow	(50)	*(50)	(50)
Femoral, leukemia mononuclear	7 (14%)	1 (2%)	13 (26%)
Femoral, vertebral, histiocytic sarcoma	1 (2%)		
Vertebral, leukemia mononuclear	7 (14%)		12 (24%)
Lymph node	(50)	*(50)	(50)
Deep cervical, leukemia mononuclear	1 (2%)		
Inguinal, leukemia mononuclear	1 (2%)		
Mandibular, leukemia mononuclear	13 (26%)	4 (8%)	18 (36%)
Mediastinal, carcinosarcoma, metastatic, lung	1 (2%)		
Mediastinal, leukemia mononuclear	12 (24%)	10 (20%)	20 (40%)
Pancreatic, leukemia mononuclear	3 (6%)	2 (4%)	
Renal, leukemia mononuclear	1 (2%)	2 (4%)	2 (4%)
Lymph node, mesenteric	(15)	*(50)	(8)
Leukemia mononuclear	6 (40%)	3 (6%)	5 (63%)
Spleen	(50)	(47)	(50)
Hemangioma	1 (2%)		
Leukemia mononuclear	18 (36%)	18 (38%)	24 (48%)
Sarcoma	1 (2%)		
Thymus	(37)	*(50)	(35)
Leukemia mononuclear	5 (14%)	2 (4%)	3 (9%)
INTEGUMENTARY SYSTEM			
Mammary gland	(37)	*(50)	(39)
Adenocarcinoma			1 (3%)
Adenoma			1 (3%)
Fibroadenoma	2 (5%)	1 (2%)	1 (3%)
Leukemia mononuclear	1 (3%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM (Continued)			
Skin	(50)	*(50)	(50)
Basal cell adenoma	1 (2%)	1 (2%)	1 (2%)
Basosquamous tumor benign	1 (2%)		
Keratoacanthoma	1 (2%)	6 (12%)	3 (6%)
Leukemia mononuclear	1 (2%)		
Papilloma squamous	1 (2%)	2 (4%)	
Sebaceous gland, adenoma	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	3 (6%)	1 (2%)	2 (4%)
Subcutaneous tissue, fibroma, multiple		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
NERVOUS SYSTEM			
Brain	(48)	*(50)	(50)
Astrocytoma malignant			1 (2%)
Carcinoma, metastatic, pituitary gland			1 (2%)
Glioma malignant		1 (2%)	
Leukemia mononuclear	3 (6%)	1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)		
Carcinosarcoma	1 (2%)		
Leukemia mononuclear	14 (28%)	7 (14%)	20 (41%)
Pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)		
Nose	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)		
Nasolacrimal duct, squamous cell carcinoma	1 (2%)		
SPECIAL SENSES SYSTEM			
Zymbal gland	(50)	*(50)	*(50)
Adenoma	1 (2%)		
Carcinoma			1 (2%)
URINARY SYSTEM			
Kidney	(50)	*(50)	(50)
Leukemia mononuclear	12 (24%)	14 (28%)	20 (40%)
Pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)		
Urinary bladder	(50)	*(50)	(49)
Leukemia mononuclear	3 (6%)		
Mesothelioma malignant		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	18 (36%)	18 (36%)	24 (48%)
Mesothelioma malignant	1 (2%)	1 (2%)	2 (4%)
Hemangioma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	28	21	27
Moribund	15	22	19
Dead	7	7	4
TUMOR SUMMARY			
Total animals with primary neoplasms **	49	49	49
Total primary neoplasms	132	109	129
Total animals with benign neoplasms	48	48	49
Total benign neoplasms	105	84	98
Total animals with malignant neoplasms	23	23	29
Total malignant neoplasms	27	25	31
Total animals with secondary neoplasms ***	3		1
Total secondary neoplasms	3		1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: VEHICLE CONTROL

WEEKS ON STUDY	059	061	074	076	080	085	085	090	090	091	094	096	097	097	099	099	100	102	102	103	103	104	105	105	105
CARCASS ID	045	062	035	085	074	034	043	033	104	025	044	244	052	095	102	032	051	014	064	081	083	094	113	115	021
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear					X				X		X	X	X		X		X		X	X		X		X	X
Neoplastic nodule																									
Mesentery	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear												X	X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X	X													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Leukemia mononuclear													X												
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X	X	X		X							X			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X		X	X	X		X		X		X	X		X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X		X	X	X		X		X		X	X		X			
Pheochromocytoma malignant		X												X											
Pheochromocytoma benign																		X	X	X		X			
Bilateral, pheochromocytoma benign										X			X			X					X				X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X								X			X		X			
Pars distalis, adenoma	X		X		X	X	X						X				X					X		X	
Pars distalis, adenoma, multiple																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma							X			X				X	X										X
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland	+	+	+	+		+	+			+	+	+		+		+	+				+	+		+	+
Ductus deferens		+	+		+			+	+			+							+					+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis											+								+	+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Adenoma															X			X							
Leukemia mononuclear												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Seminal vesicle			+	+		+						+	+	+	+		+			+		+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant											X														
Bilateral, interstitial cell, adenoma							X	X	X	X	X	X		X	X			X	X			X	X		X
Interstitial cell, adenoma													X			X	X			X	X				

\- Tissue examined microscopically
Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	041	042	061	082	084	091	092	093	022	031	054	065	071	073	075	111	123	233	535	555	663	672	101	103	105	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Leukemia mononuclear	X							X					X		X	X										17
Neoplastic nodule								X		X					X		X									4
Mesentery	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Papilloma squamous																					X					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X					X													12
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Leukemia mononuclear								X					X													12
Pheochromocytoma malignant																										2
Pheochromocytoma benign		X	X	X	X									X	X											10
Bilateral, pheochromocytoma benign										X	X							X								8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X																								1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Pars distalis, adenoma						X	X	X		X					X	X		X					X		X	18
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X			X	7
C-cell, carcinoma									X																	1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+		+	+	+	+		+		+	+	+	+		+		+	+		+	36
Ductus deferens	+						+			+				+		+									+	15
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Leukemia mononuclear																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Seminal vesicle	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+		+	+	+	+	+	+	35
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X		X		33
Interstitial cell, adenoma			X							X																7

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	059	061	074	076	080	085	085	090	090	091	094	096	097	097	099	099	100	102	102	103	103	104	105	105	105
CARCASS ID	045	062	035	085	074	034	043	033	104	025	044	024	052	095	102	032	051	014	064	081	083	094	013	115	021
HEMATOPOIETIC SYSTEM																									
Blood									+																
Leukemia mononuclear									X																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear									X		X	X			X		X		X			X			
Femoral, vertebral, histiocytic sarcoma																									
Vertebral, leukemia mononuclear									X		X	X			X		X		X			X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, leukemia mononuclear												X													
Inguinal, leukemia mononuclear												X													
Mandibular, leukemia mononuclear					X				X		X	X	X		X		X		X	X		X			
Mediastinal, carcinosarcoma, metastatic, lung							X																		
Mediastinal, leukemia mononuclear					X				X		X	X	X		X		X		X	X		X			X
Pancreatic, leukemia mononuclear												X							X						
Renal, leukemia mononuclear															X										
Lymph node, mesenteric	M	M	M	M	+	+	M	M	+	M	+	+	M	+	+	+	M	+	M	M	+	M	+	M	M
Leukemia mononuclear					X				X		X	X			X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Leukemia mononuclear					X				X		X	X	X		X		X		X	X		X		X	X
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	M	+	M	M	+
Leukemia mononuclear					X						X		X						X			X			
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+		+	+	+	+	M	+	+	+	+	M	M	+	M	M	+	+	+	+	M	+
Fibroadenoma																									
Leukemia mononuclear												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basosquamous tumor benign									X																
Keratoacanthoma																									
Leukemia mononuclear												X													
Papilloma squamous																									
Sebaceous gland, adenoma																X									
Subcutaneous tissue, fibroma								X		X				X											
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
NERVOUS SYSTEM																									
Brain	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X		X		X								
Peripheral nerve	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinosarcoma							X																		
Leukemia mononuclear					X				X		X	X	X		X		X		X	X		X			X
Pheochromocytoma malignant, metastatic, adrenal gland		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X	X												
Nasolacrimal duct, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye									+										+	+					
Harderian gland	+					+	+	+	+	+										+					
Zymbal gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X		X	X	X		X		X		X	X		X			X
Pheochromocytoma malignant, metastatic, adrenal gland														X											
Ureter	+	+		+	+	+	+	+	+		+	+		+		+		+	+	+		+	+		+
Urethra					+				+		+		+			+	+	+	+						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X	X					X								

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	041	042	061	082	084	091	092	093	022	031	054	065	071	073	075	111	112	023	053	055	063	072	101	103	105	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										7
Femoral, vertebral, histiocytic sarcoma																				X						1
Vertebral, leukemia mononuclear																										7
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deep cervical, leukemia mononuclear																										1
Inguinal, leukemia mononuclear																										1
Mandibular, leukemia mononuclear								X					X		X											13
Mediastinal, carcinosarcoma, metastatic, lung																										1
Mediastinal, leukemia mononuclear								X																		12
Pancreatic, leukemia mononuclear																X										3
Renal, leukemia mononuclear																										1
Lymph node, mesenteric	M	+	M	M	M	M	M	+	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M	15
Leukemia mononuclear								X																		6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma					X																					1
Leukemia mononuclear	X		X					X					X		X	X										18
Sarcoma	X																									1
Thymus	+	M	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	M	37
Leukemia mononuclear																										5
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	37
Fibroadenoma			X																						X	2
Leukemia mononuclear																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma															X											1
Basosquamous tumor benign																										1
Keratoacanthoma														X												1
Leukemia mononuclear																										1
Papilloma squamous																						X				1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma																										3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										3
Peripheral nerve	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Carcinosarcoma																										1
Leukemia mononuclear								X					X		X											14
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Nasolacrimal duct, squamous cell carcinoma								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye		I																								3
Harderian gland																						+				8
Zymbal gland													+													1
Adenoma													X													1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		12
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Ureter	+	+		+	+			+		+	+	+	+	+	+	+		+			+	+	+	+		35
Urethra		+							+		+			+		+	+		+			+			+	18
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: LOW DOSE

WEEKS ON STUDY	05 5	05 9	06 1	07 1	07 3	07 4	07 4	07 9	08 0	08 1	08 3	08 6	08 6	08 6	08 6	08 7	09 2	09 2	09 7	09 7	09 8	09 9	10 0	10 0	10 2
CARCASS ID	27 5	25 5	22 5	29 5	28 5	23 3	23 5	21 2	21 3	22 1	22 4	27 3	29 4	23 1	27 2	26 5	23 4	27 4	24 4	25 1	28 4	24 3	22 3	30 3	26 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine large	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Intestine large, cecum	+	A	+	A	+	+	+	+	+	A	+	+	A	+	+	+									
Intestine large, colon	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Mesothelioma malignant				X																					
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Mesothelioma malignant				X																					
Intestine small	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Intestine small, ileum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Mesothelioma malignant				X																					
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Mesothelioma malignant				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear					X	X			X		X		X		X			X	X		X		X	X	
Neoplastic nodule																									
Mesentery	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+							
Mesothelioma malignant				X																					
Pancreas	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Leukemia mononuclear															X										
Mesothelioma malignant				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+									
Stomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Stomach, glandular	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+				+	+	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear					X								X		X								X	X	
Adrenal gland medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X								X		X								X	X	
Pheochromocytoma malignant																									
Pheochromocytoma benign																X			X						
Islets, pancreatic	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+									
Pituitary gland	+	I	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+			+			+		+
Pars distalis, adenoma			X		X		X			X		X				X	X			X			X		X
Thyroid gland	+	A	+	+	+	+	+	+	+	A	+	+	M	+	+	+							+		
C cell, adenoma																X									
Follicular cell, carcinoma																							X		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland	+			+	+	+		+	+	+	+	+	+	+	+	+									
Ductus deferens			+		+				+	+	+					+									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Mesothelioma malignant				X																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Adenoma														X											
Squamous cell carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									+
Seminal vesicle	+			+	+	+	+	+		+	+	+	+	+	+	+						+			+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+
Bilateral, mesothelioma malignant				X																					
Bilateral, interstitial cell adenoma						X		X							X			X			X	X	X	X	
Interstitial cell, adenoma				X					X	X	X		X	X		X	X								

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	232	261	281	245	252	262	282	302	304	214	215	222	241	242	253	283	291	292	301	211	254	263	271	293	305		TOTAL. TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											16
Intestine large																											15
Intestine large, cecum																											12
Intestine large, colon																											14
Mesothelioma malignant																											1
Intestine large, rectum																											15
Mesothelioma malignant																											1
Intestine small																											14
Intestine small, duodenum																											14
Intestine small, ileum																											14
Mesothelioma malignant																											1
Intestine small, jejunum																											14
Mesothelioma malignant																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma	X																										1
Leukemia mononuclear			X		X		X				X						X	X	X								18
Neoplastic nodule						X																					1
Mesentery																											16
Mesothelioma malignant																											1
Pancreas	+											+			+												17
Leukemia mononuclear																											1
Mesothelioma malignant																											1
Salivary glands																											15
Stomach																											15
Stomach, forestomach																											15
Stomach, glandular																											14
Tooth																											16
CARDIOVASCULAR SYSTEM																											
Blood vessel																											16
Heart																		+									21
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma				X					X																		2
Leukemia mononuclear			X														X										7
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear			X														X										7
Pheochromocytoma malignant											X											X					2
Pheochromocytoma benign		X				X		X					X						X								7
Islets, pancreatic																											14
Parathyroid gland																											14
Pituitary gland	+			+	+				+						+							+			+		23
Pars distalis, adenoma	X								X						X							X					14
Thyroid gland				+		+		+																			17
C cell, adenoma				X		X		X																			4
Follicular cell, carcinoma																											1
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Coagulating gland																											13
Ductus deferens																											6
Epididymis																											16
Mesothelioma malignant																											1
Preputial gland			+																								17
Adenoma			X																								2
Squamous cell carcinoma																											1
Prostate	+														+												19
Seminal vesicle															+												16
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Bilateral, mesothelioma malignant																											1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		33
Interstitial cell, adenoma																											8

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	055	059	061	071	073	074	074	079	080	081	083	086	086	086	086	087	092	092	097	097	098	099	100	100	102
CARCASS ID	275	255	225	295	285	233	235	212	213	221	224	273	294	231	272	265	234	274	444	251	284	243	223	303	264
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Femoral, leukemia mononuclear									X																
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						+	+	
Mandibular, leukemia mononuclear											X				X								X		
Mediastinal, leukemia mononuclear					X	X			X		X				X								X	X	
Pancreatic, leukemia mononuclear					X										X										
Renal, leukemia mononuclear															X										
Lymph node, mesenteric	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+						+		
Leukemia mononuclear											X												X		
Spleen	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	X	X	+	+	+	+	+
Leukemia mononuclear					X	X			X		X		X		X							X	X	X	
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+									
Leukemia mononuclear											X				X										
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+				
Basal cell adenoma																									
Keratoacanthoma																X									
Papilloma squamous																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibroma, multiple								X																	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Glioma malignant	X																								
Leukemia mononuclear													X												
Peripheral nerve	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+									
Spinal cord	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Leukemia mononuclear					X	X			X		X		X		X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+									
SPECIAL SENSES SYSTEM																									
Eye			+		+	+												+							
Harderian gland	M	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+		+	+			+	+		+
Leukemia mononuclear					X	X			X		X		X		X			X	X				X		
Ureter	+		+	+	+	+		+	+	A	+		+	+	+	+									
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+						+			+
Mesothelioma malignant				X																					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	232	261	281	245	252	262	282	302	304	214	215	222	241	242	253	283	291	292	301	211	254	263	271	293	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										16
Femoral, leukemia mononuclear																										1
Lymph node	+	+	+								+				+		+									25
Mandibular, leukemia mononuclear											X															4
Mediastinal, leukemia mononuclear			X								X						X									10
Pancreatic, leukemia mononuclear																										2
Renal, leukemia mononuclear											X															2
Lymph node, mesenteric	+										+				+											6
Leukemia mononuclear											X															3
Spleen	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear			X		X		X				X						X	X	X							18
Thymus																										14
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland									+														+			15
Fibroadenoma																							X			1
Skin		+	+		+		+		+								+	+					+			25
Basal cell adenoma					X																					1
Keratoacanthoma		X	X		X		X		X																	6
Papilloma squamous																	X	X								2
Sebaceous gland, adenoma									X																	1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibroma, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										16
Skeletal muscle																										16
NERVOUS SYSTEM																										
Brain																										16
Glioma malignant																										1
Leukemia mononuclear																										1
Peripheral nerve																										15
Spinal cord																										15
RESPIRATORY SYSTEM																										
Lung			+																							17
Leukemia mononuclear			X																							7
Nose																										16
Trachea																										15
SPECIAL SENSES SYSTEM																										
Eye									+	+																6
Harderian gland																										12
URINARY SYSTEM																										
Kidney	+		+		+	+	+		+	+	+				+	+	+	+	+	+	+			+		36
Leukemia mononuclear			X								X						X	X	X							14
Ureter																										12
Urinary bladder																+										18
Mesothelioma malignant																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF N-METHYLOLACRYLAMIDE: HIGH DOSE

WEEKS ON STUDY	053	061	070	079	080	082	087	090	094	094	094	099	100	100	102	102	102	102	102	103	104	104	104	104	104	105	105
CARCASS ID	445	555	484	443	425	411	462	465	463	503	453	481	433	504	432	471	482	454	494	473	444	434	491	412	413
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X	X	X					X			X	X	X	X		X	X	X	
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X	X					X				X		X		X		X	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Leukemia mononuclear				X			X	X	X					X					X	X		X	X	X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X					X					X	X		X	X	X	
Pheochromocytoma benign										X			X	X				X		X		X			
Bilateral, pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X												X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X									X			
Pars distalis, adenoma		X								X	X		X	X	X							X			X
Pars distalis, carcinoma												X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X	X				X			X								X								
C-cell, carcinoma																										
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland	+	+	+	+	+	+		+		+		+		+			+		+					+	+
Ductus deferens	+		+			+		+		+			+			+								+	+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																										
Penis															+											
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma				X																	X					
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+		+		+	+	+	+	+	+				+		+		+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																										
Bilateral, interstitial cell, adenoma				X				X					X	X	X	X	X	X	X	X		X	X	X	X	
Interstitial cell, adenoma			X		X	X	X		X			X									X					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	422	442	452	461	474	493	501	505	423	431	441	451	464	475	483	502	411	415	421	424	435	472	485	492	495	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X	X	X		X	X				X		X				X		X		X		24
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+																							1
Papilloma squamous			X																							1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear														X												9
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear							X							X		X						X		X		15
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X							X		X						X		X		15
Pheochromocytoma benign											X		X							X			X		X	11
Bilateral, pheochromocytoma benign										X																2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Parathyroid gland	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear														X												3
Pars distalis, adenoma	X								X							X					X	X				13
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma														X		X	X					X				9
C-cell, carcinoma																							X			1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland	+	+			+	+	+		+		+	+	+	+	+	+	+	+				+	+	+	+	32
Ductus deferens		+	+	+		+	+	+							+			+	+						+	19
Epididymis	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant	X																									1
Penis											+															2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma															X											3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+		+	+	+	+	+	+	+	40
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant	X					X																				2
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	38
Interstitial cell, adenoma	X																									8

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	053	061	070	079	080	082	087	090	094	094	094	099	100	100	102	102	102	102	102	103	104	104	104	104	105	105
CARCASS ID	445	455	484	443	425	411	462	465	463	503	453	481	433	504	432	471	482	454	494	473	444	434	491	412	413
HEMATOPOIETIC SYSTEM																										
Blood					+			+																		
Leukemia mononuclear					X			X																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear				X	X		X	X									X			X		X		X		
Vertebral, leukemia mononuclear				X	X			X									X			X		X		X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, leukemia mononuclear					X		X	X	X					X			X	X	X	X		X	X	X		
Mediastinal, leukemia mononuclear					X		X	X	X					X				X	X	X		X	X	X		
Renal, leukemia mononuclear																		X	X							
Lymph node, mesenteric	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	+	+	+	M	M	M	M	M	M	M
Leukemia mononuclear								X										X	X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X	X	X					X			X	X	X	X		X	X	X		
Thymus	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	M	+	+	+	M	+	M	+	M	+	
Leukemia mononuclear					X		X																			
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	M	+	+	M	M	M	+	M	+	+	+	+	+	+	+	
Adenocarcinoma																	X									
Adenoma																					X					
Fibroadenoma																									X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Basal cell adenoma																										
Keratoacanthoma													X		X					X						
Sebaceous gland, adenoma												X														
Subcutaneous tissue, fibroma						X																				
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Astrocytoma malignant			X																							
Carcinoma, metastatic, pituitary gland												X														
Peripheral nerve	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X		X	X	X					X			X	X	X	X		X	X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																										
Ear																					+					
Eye				+				+											+							
Harderian gland	+	+		+				+	+		+															
Zymbal gland																										
Carcinoma																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X		X	X	X					X			X	X	X	X		X	X	X		
Ureter	+	+	+	+	+	+		+		+	+		+	+		+	+				+	+	+	+	+	
Urethra									+		+				+	+	+		+	+		+	+			
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	422	442	452	461	474	493	501	505	423	431	441	451	464	475	483	502	414	415	421	424	435	472	485	492	495	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Leukemia mononuclear																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear							X							X						X		X		X		13
Vertebral, leukemia mononuclear							X							X						X		X		X		12
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandibular, leukemia mononuclear		X					X				X					X				X		X				18
Mediastinal, leukemia mononuclear		X			X		X			X				X		X				X		X		X		20
Renal, leukemia mononuclear																										2
Lymph node, mesenteric	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	8
Leukemia mononuclear		X																		X						5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X	X	X			X	X			X		X				X		X		X		24
Thymus	M	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+	35
Leukemia mononuclear														X												3
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M	+	+	M	+	39
Adenocarcinoma																										1
Adenoma																										1
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma				X																						1
Keratoacanthoma																										3
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma																				X						2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Carcinoma, metastatic, pituitary gland																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	46
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X					X			X				X		X				X		X		X		20
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye			+		+							+														6
Harderian gland																					+		+			8
Zymbal gland								+																		1
Carcinoma								X																		1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X		X				X			X						X		X		X		20
Ureter	+	+	+	+	+		+	+	+			+	+	+	+		+	+	+	+	+				+	36
Urethra		+				+		+			+					+	+	+	+						+	19
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	6 mg/kg	12 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	18/49 (37%)	7/50 (14%)	13/50 (26%)
Adjusted Rates (b)	50.7%	26.2%	36.9%
Terminal Rates (c)	10/27 (37%)	4/22 (18%)	6/27 (22%)
Day of First Observation	637	608	654
Life Table Tests (d)	P=0.161N	P=0.051N	P=0.198N
Logistic Regression Tests (d)	P=0.115N	P=0.022N	P=0.143N
Cochran-Armitage Trend Test (d)	P=0.136N		
Fisher Exact Test (d)		P=0.008N	P=0.175N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	20/49 (41%)	9/50 (18%)	13/50 (26%)
Adjusted Rates (b)	53.0%	34.4%	36.9%
Terminal Rates (c)	10/27 (37%)	6/22 (27%)	6/27 (22%)
Day of First Observation	422	608	654
Life Table Tests (d)	P=0.088N	P=0.070N	P=0.115N
Logistic Regression Tests (d)	P=0.055N	P=0.024N	P=0.078N
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.011N	P=0.088N
Preputial Gland: Adenoma			
Overall Rates (a)	2/49 (4%)	(e) 2/17 (12%)	3/48 (6%)
Adjusted Rates (b)	5.9%		8.9%
Terminal Rates (c)	0/27 (0%)		1/27 (4%)
Day of First Observation	688		548
Life Table Test (d)			P=0.528
Logistic Regression Test (d)			P=0.488
Fisher Exact Test (d)			P=0.490
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	14.3%	4.5%	0.0%
Terminal Rates (c)	4/28 (14%)	1/22 (5%)	0/27 (0%)
Day of First Observation	731	731	
Life Table Tests (d)	P=0.031N	P=0.255N	P=0.066N
Logistic Regression Tests (d)	P=0.031N	P=0.255N	P=0.066N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.181N	P=0.059N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	14.3%	8.4%	0.0%
Terminal Rates (c)	4/28 (14%)	1/22 (5%)	0/27 (0%)
Day of First Observation	731	722	
Life Table Tests (d)	P=0.044N	P=0.445N	P=0.066N
Logistic Regression Tests (d)	P=0.041N	P=0.448N	P=0.066N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.339N	P=0.059N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	7.1%	4.5%	9.5%
Terminal Rates (c)	2/28 (7%)	1/22 (5%)	1/27 (4%)
Day of First Observation	731	731	708
Life Table Tests (d)	P=0.402	P=0.585N	P=0.501
Logistic Regression Tests (d)	P=0.417	P=0.585N	P=0.516
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	6 mg/kg	12 mg/kg
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	19/50 (38%)	(e) 14/23 (61%)	13/50 (26%)
Adjusted Rates (b)	49.1%		35.4%
Terminal Rates (c)	10/28 (36%)		6/27 (22%)
Day of First Observation	410		425
Life Table Test (d)			P=0.172N
Logistic Regression Test (d)			P=0.143N
Fisher Exact Test (d)			P=0.142N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	19/50 (38%)	(e) 14/23 (61%)	14/50 (28%)
Adjusted Rates (b)	49.1%		37.1%
Terminal Rates (c)	10/28 (36%)		6/27 (22%)
Day of First Observation	410		425
Life Table Test (d)			P=0.226N
Logistic Regression Test (d)			P=0.199N
Fisher Exact Test (d)			P=0.198N
Skin: Keratoacanthoma			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	3.6%	23.1%	8.4%
Terminal Rates (c)	1/28 (4%)	3/22 (14%)	0/27 (0%)
Day of First Observation	731	608	695
Life Table Tests (d)	P=0.291	P=0.033	P=0.323
Logistic Regression Tests (d)	P=0.286	P=0.035	P=0.311
Cochran-Armitage Trend Test (d)	P=0.274		
Fisher Exact Test (d)		P=0.056	P=0.309
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.3%	5.5%	5.8%
Terminal Rates (c)	0/28 (0%)	0/22 (0%)	1/27 (4%)
Day of First Observation	624	549	573
Life Table Tests (d)	P=0.403N	P=0.570N	P=0.496N
Logistic Regression Tests (d)	P=0.405N	P=0.438N	P=0.501N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	40/50 (80%)	41/48 (85%)	46/50 (92%)
Adjusted Rates (b)	90.9%	100.0%	100.0%
Terminal Rates (c)	24/28 (86%)	22/22 (100%)	27/27 (100%)
Day of First Observation	593	492	487
Life Table Tests (d)	P=0.186	P=0.087	P=0.201
Logistic Regression Tests (d)	P=0.021	P=0.041	P=0.044
Cochran-Armitage Trend Test (d)	P=0.057		
Fisher Exact Test (d)		P=0.330	P=0.074
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/50 (14%)	(e) 4/17 (24%)	9/50 (18%)
Adjusted Rates (b)	19.5%		24.4%
Terminal Rates (c)	3/28 (11%)		4/27 (15%)
Day of First Observation	593		425
Life Table Test (d)			P=0.402
Logistic Regression Test (d)			P=0.388
Fisher Exact Test (d)			P=0.393

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	6 mg/kg	12 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	(e) 4/17 (24%)	10/50 (20%)
Adjusted Rates (b)	22.7%		27.7%
Terminal Rates (c)	4/28 (14%)		5/27 (19%)
Day of First Observation	593		425
Life Table Test (d)			P=0.402
Logistic Regression Test (d)			P=0.393
Fisher Exact Test (d)			P=0.398
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	18/50 (36%)	18/50 (36%)	24/50 (48%)
Adjusted Rates (b)	46.1%	49.2%	60.3%
Terminal Rates (c)	8/28 (29%)	6/22 (27%)	12/27 (44%)
Day of First Observation	554	509	548
Life Table Tests (d)	P=0.185	P=0.333	P=0.200
Logistic Regression Tests (d)	P=0.133	P=0.547	P=0.159
Cochran-Armitage Trend Test (d)	P=0.131		
Fisher Exact Test (d)		P=0.582N	P=0.156

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues

TABLE A4a. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence of Keratoacanthomas in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	3/50
Malonaldehyde, sodium salt (c)	3/50
Chlorpheniramine maleate (c)	1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	1/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	2/50
Methyl carbamate (d)	0/50
TOTAL	10/300 (3.3%)
SD (e)	2.42%
Range (f)	
High	3/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	31/1,936 (1.6%)
SD (e)	2.98%
Range (f)	
High	7/49
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	46/50
Malonaldehyde, sodium salt (c)	40/50
Chlorpheniramine maleate (c)	44/49
Tetrakis(hydroxymethyl)phosphonium chloride (c)	44/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	40/50
Methyl carbamate (d)	43/50
TOTAL	257/299 (86.0%)
SD (e)	5.03%
Range (f)	
High	46/50
Low	40/50
Overall Historical Incidence for Untreated Controls	
TOTAL	1,677/1,910 (87.8%)
SD (e)	7.70%
Range (f)	
High	49/50
Low	32/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(16)	(50)
Foreign body		1 (6%)	
Inflammation, necrotizing	1 (2%)		
Intestine large, colon	(49)	(14)	(50)
Parasite metazoan	4 (8%)		6 (12%)
Intestine large, rectum	(49)	(15)	(49)
Inflammation, chronic active		1 (7%)	
Parasite metazoan	3 (6%)	1 (7%)	4 (8%)
Liver	(50)	(50)	(50)
Basophilic focus	7 (14%)	14 (28%)	5 (10%)
Clear cell focus	1 (2%)	1 (2%)	1 (2%)
Clear cell focus, multiple			1 (2%)
Degeneration, cystic	10 (20%)	8 (16%)	19 (38%)
Eosinophilic focus			1 (2%)
Fatty change	2 (4%)		
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic	3 (6%)	7 (14%)	7 (14%)
Inflammation, necrotizing	1 (2%)		
Leukocytosis		1 (2%)	
Mineralization	1 (2%)		1 (2%)
Necrosis, coagulative	2 (4%)	2 (4%)	5 (10%)
Vacuolization cytoplasmic	1 (2%)	4 (8%)	1 (2%)
Pancreas	(50)	(17)	(50)
Cyst		1 (6%)	
Inflammation, chronic	1 (2%)		
Pigmentation, hemosiderin			1 (2%)
Acinus, atrophy	15 (30%)	9 (53%)	15 (30%)
Acinus, hyperplasia			1 (2%)
Artery, inflammation, proliferative		3 (18%)	
Salivary glands	(50)	(15)	(49)
Inflammation, chronic active			1 (2%)
Stomach, forestomach	(50)	(15)	(50)
Inflammation, chronic active	2 (4%)	2 (13%)	1 (2%)
Mineralization			1 (2%)
Epithelium, hyperplasia		1 (7%)	
Stomach, glandular	(50)	(14)	(50)
Mineralization	1 (2%)		3 (6%)
Necrosis, coagulative	1 (2%)		
Tooth	(49)	(16)	(50)
Inflammation, suppurative	1 (2%)		
CARDIOVASCULAR SYSTEM			
Blood vessel	(49)	(16)	(48)
Aorta, mineralization			1 (2%)
Mesenteric artery, mineralization	1 (2%)		
Mesenteric artery, intima, proliferation	1 (2%)		
Pulmonary artery, mineralization			1 (2%)
Heart	(50)	(21)	(50)
Cardiomyopathy, chronic	48 (96%)	16 (76%)	48 (96%)
Infarct	1 (2%)		
Mineralization	3 (6%)		
Atrium, thrombus	3 (6%)	6 (29%)	1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)
Mineralization		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)
Degeneration, fatty	8 (16%)	12 (24%)	9 (18%)
Hyperplasia	10 (20%)	10 (20%)	15 (30%)
Hypertrophy	1 (2%)	2 (4%)	4 (8%)
Necrosis, coagulative	1 (2%)		
Adrenal gland, medulla	(49)	(50)	(50)
Angiectasis	1 (2%)		
Atypical cells		1 (2%)	
Hyperplasia	13 (27%)	24 (48%)	16 (32%)
Necrosis, coagulative			2 (4%)
Islets, pancreatic	(50)	(14)	(50)
Vacuolization cytoplasmic		1 (7%)	
Parathyroid gland	(48)	(14)	(45)
Hyperplasia	1 (2%)	2 (14%)	3 (7%)
Pituitary gland	(50)	(23)	(50)
Pars distalis, cyst	4 (8%)	1 (4%)	2 (4%)
Pars distalis, hyperplasia	18 (36%)	3 (13%)	15 (30%)
Pars distalis, pigmentation, hemosiderin	1 (2%)		
Pars intermedia, angiectasis			1 (2%)
Pars intermedia, cyst	2 (4%)		2 (4%)
Thyroid gland	(50)	(17)	(50)
Mineralization	1 (2%)		
C-cell, hyperplasia	9 (18%)	5 (29%)	17 (34%)
Follicular cell, hyperplasia	1 (2%)	7 (41%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	(36)	(13)	(32)
Inflammation, chronic active	2 (6%)		
Epididymis	(50)	(16)	(49)
Angiectasis			1 (2%)
Inflammation, chronic			1 (2%)
Pigmentation, hemosiderin			1 (2%)
Preputial gland	(49)	(17)	(48)
Hyperplasia	1 (2%)		1 (2%)
Inflammation, chronic active	42 (86%)	16 (94%)	42 (88%)
Prostate	(50)	(19)	(49)
Abscess	1 (2%)		
Atrophy			1 (2%)
Inflammation, chronic active	29 (58%)	14 (74%)	30 (61%)
Seminal vesicle	(35)	(16)	(40)
Inflammation, chronic active		1 (6%)	
Testes	(50)	(48)	(50)
Hyperplasia		2 (4%)	
Mineralization	17 (34%)	19 (40%)	10 (20%)
Interstitial cell, hyperplasia	25 (50%)	28 (58%)	27 (54%)
Perivascular, atrophy		1 (2%)	
Rete testes, hyperplasia		1 (2%)	
Seminiferous tubule, atrophy	40 (80%)	40 (83%)	46 (92%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(16)	(50)
Femoral, hyperplasia	1 (2%)		
Femoral, hyperplasia, reticulum cell	1 (2%)		1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow (Continued)	(50)	(16)	(50)
Femoral, myelofibrosis		1 (6%)	1 (2%)
Vertebral, hyperplasia	1 (2%)		
Vertebral, hyperplasia, reticulum cell			1 (2%)
Vertebral, myelofibrosis			1 (2%)
Lymph node	(50)	(25)	(50)
Bronchial, pigmentation, hemosiderin	3 (6%)		1 (2%)
Mandibular, cyst	4 (8%)		1 (2%)
Mandibular, hyperplasia, plasma cell	3 (6%)	1 (4%)	1 (2%)
Mediastinal, hemorrhage	1 (2%)		
Mediastinal, hyperplasia, plasma cell		1 (4%)	
Mediastinal, infiltration cellular, histiocytic	1 (2%)		
Mediastinal, inflammation, chronic active		1 (4%)	
Mediastinal, pigmentation, hemosiderin	1 (2%)		2 (4%)
Renal, hemorrhage	1 (2%)		
Renal, pigmentation, hemosiderin			1 (2%)
Lymph node, mesenteric	(15)	(6)	(8)
Cyst		1 (17%)	
Hemorrhage	2 (13%)		
Infiltration cellular, histiocytic	1 (7%)		
Inflammation, proliferative		1 (17%)	
Spleen	(50)	(47)	(50)
Fibrosis	5 (10%)	10 (21%)	9 (18%)
Hematopoietic cell proliferation	18 (36%)	1 (2%)	8 (16%)
Hyperplasia, lymphoid		1 (2%)	
Infarct			1 (2%)
Infiltration cellular, lipocyte	1 (2%)		
Necrosis, coagulative	1 (2%)		
Pigmentation, hemosiderin			3 (6%)
Thymus	(37)	(14)	(35)
Cyst	3 (8%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(37)	(15)	(39)
Hyperplasia, cystic	37 (100%)	12 (80%)	36 (92%)
Skin	(50)	(25)	(50)
Cyst epithelial inclusion		1 (4%)	
Fibrosis			1 (2%)
Inflammation, chronic active	2 (4%)	2 (8%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(16)	(50)
Cranium, fibrous osteodystrophy	1 (2%)		2 (4%)
Femur, fibrous osteodystrophy	1 (2%)		2 (4%)
Vertebra, fibrous osteodystrophy	1 (2%)		2 (4%)
NERVOUS SYSTEM			
Brain	(48)	(16)	(50)
Compression	4 (8%)	4 (25%)	9 (18%)
Hemorrhage	3 (6%)	1 (6%)	1 (2%)
Hydrocephalus	2 (4%)	5 (31%)	2 (4%)
Inflammation, chronic	1 (2%)		
Pigmentation, hemosiderin	1 (2%)		
Thrombus			1 (2%)
White matter, degeneration	1 (2%)		
Spinal cord	(50)	(15)	(49)
Hemorrhage, acute	1 (2%)		
White matter, degeneration	19 (38%)		21 (43%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(17)	(49)
Bacterium		1 (6%)	
Granuloma		2 (12%)	
Inflammation, chronic active	4 (8%)	2 (12%)	1 (2%)
Metaplasia, osseous		1 (6%)	
Mineralization	1 (2%)		
Alveolar epithelium, hyperplasia			1 (2%)
Alveolar epithelium, hyperplasia, adenomatous	3 (6%)	2 (12%)	3 (6%)
Artery, mediastinum, necrosis, fibrinoid	1 (2%)		1 (2%)
Interstitium, inflammation, chronic			4 (8%)
Mediastinum, inflammation, chronic active	1 (2%)		1 (2%)
Nose	(50)	(16)	(50)
Inflammation, chronic active	4 (8%)	1 (6%)	2 (4%)
Inflammation, suppurative		1 (6%)	
Nasolacrimal duct, inflammation, chronic	15 (30%)		12 (24%)
Nasolacrimal duct, inflammation, suppurative	4 (8%)		3 (6%)
Trachea	(50)	(15)	(50)
Inflammation, chronic active	1 (2%)	1 (7%)	
SPECIAL SENSES SYSTEM			
Eye	(3)	(6)	(6)
Hemorrhage		1 (17%)	1 (17%)
Lens, cataract	1 (33%)	1 (17%)	2 (33%)
Retina, atrophy	1 (33%)	2 (33%)	2 (33%)
Harderian gland	(8)	(12)	(8)
Hemorrhage			1 (13%)
URINARY SYSTEM			
Kidney	(50)	(36)	(50)
Cyst	6 (12%)	8 (22%)	6 (12%)
Hydronephrosis	1 (2%)		
Inflammation, chronic		1 (3%)	
Mineralization	1 (2%)		
Nephropathy, chronic	50 (100%)	36 (100%)	50 (100%)
Urinary bladder	(50)	(18)	(49)
Inflammation, chronic active	1 (2%)	2 (11%)	1 (2%)
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, duodenum	(49)	*(50)	(50)
Leukemia mononuclear		1 (2%)	
Intestine small, ileum	(46)	*(50)	(48)
Leukemia mononuclear		1 (2%)	1 (2%)
Intestine small, jejunum	(48)	*(50)	(48)
Leukemia mononuclear		1 (2%)	
Liver	(50)	*(50)	(50)
Leukemia mononuclear	14 (28%)	8 (16%)	14 (28%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear		2 (4%)	1 (2%)
Pancreas	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	
Salivary glands	(50)	*(50)	(50)
Leukemia mononuclear		1 (2%)	
Stomach, forestomach	(49)	*(50)	(50)
Papilloma squamous		1 (2%)	
Stomach, glandular	(49)	*(50)	(50)
Leukemia mononuclear			1 (2%)
Tongue	*(50)	*(50)	*(50)
Squamous cell carcinoma			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)		6 (12%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)
Leukemia mononuclear	4 (8%)	8 (16%)	4 (8%)
Adrenal gland, medulla	(50)	(50)	(50)
Leukemia mononuclear	4 (8%)	8 (16%)	4 (8%)
Pheochromocytoma benign	1 (2%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	*(50)	(50)
Adenoma			2 (4%)
Parathyroid gland	(34)	*(50)	(42)
Adenoma			1 (2%)
Pituitary gland	(49)	*(50)	(50)
Leukemia mononuclear	3 (6%)	2 (4%)	4 (8%)
Pars distalis, adenoma	19 (39%)	19 (38%)	14 (28%)
Pars distalis, leukemia mononuclear		2 (4%)	
Thyroid gland	(50)	*(50)	(50)
C-cell, adenoma	11 (22%)	2 (4%)	7 (14%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma	2 (4%)		2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(45)	*(50)	(50)
Adenoma	2 (4%)	2 (4%)	4 (8%)
Leukemia mononuclear	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Ovary	(50)	*(50)	(50)
Granulosa cell tumor benign	1 (2%)		
Leukemia mononuclear	2 (4%)	1 (2%)	2 (4%)
Uterus	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)		
Polyp	1 (2%)		1 (2%)
Polyp stromal	6 (12%)	2 (4%)	6 (12%)
Polyp stromal, multiple	1 (2%)		2 (4%)
Sarcoma stromal		3 (6%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(50)
Femoral, leukemia mononuclear	2 (4%)	1 (2%)	3 (6%)
Vertebral, leukemia mononuclear	1 (2%)	1 (2%)	4 (8%)
Lymph node	(50)	*(50)	(50)
Inguinal, leukemia mononuclear		1 (2%)	1 (2%)
Lumbar, leukemia mononuclear	1 (2%)	1 (2%)	
Mandibular, leukemia mononuclear	5 (10%)	2 (4%)	7 (14%)
Mediastinal, leukemia mononuclear	5 (10%)	5 (10%)	7 (14%)
Pancreatic, leukemia mononuclear		5 (10%)	1 (2%)
Renal, leukemia mononuclear	1 (2%)	1 (2%)	2 (4%)
Lymph node, mesenteric	(3)	*(50)	(6)
Leukemia mononuclear	1 (33%)	2 (4%)	5 (83%)
Spleen	(50)	*(50)	(50)
Leukemia mononuclear	14 (28%)	10 (20%)	15 (30%)
Thymus	(38)	*(50)	(41)
Leukemia mononuclear	1 (3%)	2 (4%)	1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	*(50)	(50)
Adenocarcinoma	1 (2%)	1 (2%)	1 (2%)
Fibroadenoma	15 (31%)	9 (18%)	13 (26%)
Fibroadenoma, multiple	4 (8%)		4 (8%)
Leukemia mononuclear		1 (2%)	1 (2%)
Skin	(50)	*(50)	(50)
Trichoepithelioma	1 (2%)		
Sebaceous gland, adenoma			1 (2%)
Subcutaneous tissue, fibroma		1 (2%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	
Subcutaneous tissue, myxoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Cranium, osteosarcoma		1 (2%)	
NERVOUS SYSTEM			
Spinal cord	(50)	*(50)	(50)
Leukemia mononuclear		2 (4%)	
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar carcinoma			1 (2%)
Leukemia mononuclear	7 (14%)	5 (10%)	10 (20%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Zymbal gland	(50)	*(50)	*(50)
Carcinoma	1 (2%)	1 (2%)	
URINARY SYSTEM			
Kidney	(50)	*(50)	(50)
Leukemia mononuclear	5 (10%)	4 (8%)	9 (18%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	14 (28%)	11 (22%)	15 (30%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	35	22	33
Moribund	10	20	12
Dead	5	8	5
TUMOR SUMMARY			
Total animals with primary neoplasms **	45	36	42
Total primary neoplasms	86	56	78
Total animals with benign neoplasms	39	28	36
Total benign neoplasms	68	38	60
Total animals with malignant neoplasms	18	16	18
Total malignant neoplasms	18	18	18

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: VEHICLE CONTROL

WEEKS ON STUDY	051	055	076	083	088	092	094	097	097	100	101	101	101	103	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	125	115	194	181	185	124	142	155	161	162	132	192	193	184	122	114	123	131	141	153	154	163	164	171	173
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	M	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X						X			X					
Mesentery	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X																
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Leukemia mononuclear								X	X	X	X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X														
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	M	+	M	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X															
Pars distalis, adenoma			X	X	X		X	X				X	X	X		X						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X													X					X	
C-cell, carcinoma																									
Follicular cell, adenoma						X																			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	M
Adenoma																								X	
Leukemia mononuclear									X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Leukemia mononuclear								X	X																
Oviduct	+				+	+	+		+	+		+	+	+	+		+	+	+	+				+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X																
Polyp																		X							
Polyp stromal							X			X			X											X	
Polyp stromal, multiple																									

+: Tissue examined microscopically
: Present but not examined microscopically
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	183	203	205	111	112	133	143	144	145	151	152	165	182	191	195	202	204	213	121	134	135	172	174	175	201	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X		X				X		X		X		X								14
Mesentery	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																		X			3
Leukemia mononuclear																										4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	M	+	M	M	+	+	+	+	M	M	M	+	M	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										3
Pars distalis, adenoma									X	X		X		X	X			X		X	X			X		19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X		X	X	X	X				X			X						X	11
C-cell, carcinoma																						X				1
Follicular cell, adenoma																				X						2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma	X																									2
Leukemia mononuclear																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																	X									1
Leukemia mononuclear																										2
Oviduct	+	+	+	+	+	+		+		+	+		+	+			+		+	+	+	+		+	+	34
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Polyp																										1
Polyp stromal											X		X													6
Polyp stromal, multiple								X																		1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	051	055	076	083	088	092	094	097	097	100	101	101	101	103	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	125	115	194	181	185	124	142	155	161	162	132	192	193	184	122	114	123	131	141	153	154	163	164	171	173
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear								X	X																
Vertebral, leukemia mononuclear								X																	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, leukemia mononuclear									X																
Mandibular, leukemia mononuclear								X	X	X	X														
Mediastinal, leukemia mononuclear								X	X	X	X														
Renal, leukemia mononuclear									X																
Lymph node, mesenteric	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Leukemia mononuclear									X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X						X			X					
Thymus	+	+	M	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	
Leukemia mononuclear								X																	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma			X	X	X										X	X		X	X				X		
Fibroadenoma, multiple											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
Subcutaneous tissue, fibrosarcoma	X																								
Subcutaneous tissue, myxoma						X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X						X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye								+	+								+								
Harderian gland		+		+	+	+							+			+		+							+
Zymbal gland															+										
Carcinoma															X										
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X														
Ureter				+	+			+				+											+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	183	203	205	111	112	133	143	144	145	151	152	165	182	191	195	202	204	213	221	234	235	272	274	275	201	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										2
Vertebral, leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumbar, leukemia mononuclear																										1
Mandibular, leukemia mononuclear																		X								5
Mediastinal, leukemia mononuclear	X																									5
Renal, leukemia mononuclear																										1
Lymph node, mesenteric	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	3
Leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X		X				X		X		X		X								14
Thymus	M	M	+	+	M	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	38
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma										X																1
Fibroadenoma										X				X		X				X		X			X	15
Fibroadenoma, multiple					X				X												X					4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trichoepithelioma																							X			1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, myxoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																	X								7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye									+														+			5
Harderian gland													+	+												10
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								5
Ureter				+		+	+		+			+	+	+	+		+		+		+				+	17
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: LOW DOSE

WEEKS ON STUDY	0 1 7	0 4 3	0 6 1	0 6 4	0 6 4	0 6 6	0 7 3	0 7 6	0 7 7	0 7 9	0 7 9	0 8 3	0 8 3	0 8 5	0 8 8	0 9 0	0 9 2	0 9 4	0 9 6	0 9 6	0 9 6	0 9 8	0 9 9	1 0 0
CARCASS ID	3 8 1	3 5 5	3 1 5	3 7 1	4 0 1	3 5 1	3 9 5	3 1 4	3 6 5	3 2 4	3 7 4	3 4 1	3 9 4	4 0 5	3 3 1	3 8 2	4 0 4	3 6 4	3 9 3	3 4 3	3 4 4	3 8 3	3 3 5	3 6 1
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine large, cecum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leukemia mononuclear							X																	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leukemia mononuclear							X																	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leukemia mononuclear							X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+		
Leukemia mononuclear							X				X			X		X			X			X		
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+					+
Leukemia mononuclear							X																	X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leukemia mononuclear							X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leukemia mononuclear							X																	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Papilloma squamous									X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
CARDIOVASCULAR SYSTEM																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Leukemia mononuclear							X				X					X			X			X		X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X				X					X			X			X		X
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+								
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X					X
Pars distalis, adenoma						X	X	X					X			X	X	X		X	X	X	X	
Pars distalis, leukemia mononuclear							X									X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
C-cell, adenoma												X												
GENERAL BODY SYSTEM																								
None																								
GENITAL SYSTEM																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Adenoma			X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+				+		
Leukemia mononuclear														X										
Oviduct		+										+		+		+								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Polyp stromal												X												
Sarcoma stromal						X			X															

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	102	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	342	313	353	312	322	323	354	363	385	391	332	333	352	375	402	403	311	321	325	334	345	362	372	373	392	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										16
Intestine large																									+	17
Intestine large, cecum																										14
Intestine large, colon																										16
Intestine large, rectum																									+	16
Intestine small																										16
Intestine small, duodenum																										16
Leukemia mononuclear																										1
Intestine small, ileum																										16
Leukemia mononuclear																										1
Intestine small, jejunum																										16
Leukemia mononuclear																										1
Liver	+											+														21
Leukemia mononuclear	X											X														8
Mesentery																										18
Leukemia mononuclear																										2
Pancreas												+														17
Leukemia mononuclear												X														2
Salivary glands																										16
Leukemia mononuclear																										1
Stomach																										16
Stomach, forestomach																										16
Papilloma squamous																										1
Stomach, glandular																										16
Tooth																										16
CARDIOVASCULAR SYSTEM																										
Blood vessel																										16
Heart																										16
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Leukemia mononuclear		X										X														8
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X										X														8
Pheochromocytoma benign		X																								1
Islets, pancreatic																										16
Parathyroid gland																										15
Pituitary gland		+			+	+	+	+	+		+				+	+	+		+	+	+	+	+		+	40
Leukemia mononuclear																										2
Pars distalis, adenoma		X			X	X	X		X								X		X				X			19
Pars distalis, leukemia mononuclear																										2
Thyroid gland																									+	17
C-cell, adenoma																									X	2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland										+																17
Adenoma										X																2
Ovary													+										+			20
Leukemia mononuclear																										1
Oviduct																										4
Uterus		+		+			+																			19
Polyp stromal		X																								2
Sarcoma stromal				X																						3

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	017	043	061	064	064	066	073	076	077	079	079	083	083	085	088	090	092	092	094	096	096	096	098	099	100
CARCASS ID	381	355	315	371	401	351	395	314	365	324	374	341	394	405	331	382	384	404	364	393	343	344	383	335	361
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Femoral, leukemia mononuclear							X																		
Vertebral, leukemia mononuclear							X																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+					+		+
Inguinal, leukemia mononuclear														X											
Lumbar, leukemia mononuclear							X																		
Mandibular, leukemia mononuclear							X							X											
Mediastinal, leukemia mononuclear							X				X			X									X		
Pancreatic, leukemia mononuclear							X				X			X											
Renal, leukemia mononuclear							X																		
Lymph node, mesenteric	+	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M									+
Leukemia mononuclear							X																		X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+			+		+
Leukemia mononuclear							X				X			X		X	X			X			X		X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Leukemia mononuclear							X							X											
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	+		+
Adenocarcinoma																									X
Fibroadenoma				X	X							X							X			X	X		
Leukemia mononuclear							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+		+
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma																	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Cranium, osteosarcoma										X															
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Peripheral nerve	+	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Leukemia mononuclear							X				X														
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+		
Leukemia mononuclear							X				X			X		X							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
SPECIAL SENSES SYSTEM																									
Eye											+	+								+					
Harderian gland	+	M	M	M	M	M	+	+	M	+	I	+	M	+	+	+									
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Leukemia mononuclear							X				X			X		X									
Ureter		+					+		+			+													
Urethra										+					+										
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	102	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	342	313	353	312	322	323	354	363	385	391	332	333	352	375	402	403	311	321	325	334	345	362	372	373	392	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										16
Femoral, leukemia mononuclear																										1
Vertebral, leukemia mononuclear																										1
Lymph node	+											+														21
Inguinal, leukemia mononuclear																										1
Lumbar, leukemia mononuclear																										1
Mandibular, leukemia mononuclear																										2
Mediastinal, leukemia mononuclear	X																									5
Pancreatic, leukemia mononuclear	X											X														5
Renal, leukemia mononuclear																										1
Lymph node, mesenteric																										4
Leukemia mononuclear																										2
Spleen	+	+																								22
Leukemia mononuclear	X	X																								10
Thymus																										16
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland		+											+										+			24
Adenocarcinoma																										1
Fibroadenoma		X											X										X			9
Leukemia mononuclear																										1
Skin		+											+										+			24
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										16
Cranium, osteosarcoma																										1
Skeletal muscle																										16
NERVOUS SYSTEM																										
Brain																										16
Peripheral nerve																										12
Spinal cord																										16
Leukemia mononuclear																										2
RESPIRATORY SYSTEM																										
Lung																										17
Leukemia mononuclear																										5
Nose																										16
Trachea																										16
SPECIAL SENSES SYSTEM																										
Eye	+			+																						5
Harderian gland																										8
Zymbal gland									+																	1
Carcinoma									X																	1
URINARY SYSTEM																										
Kidney																+										17
Leukemia mononuclear																										4
Ureter																										4
Urethra																										2
Urinary bladder																										14

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: HIGH DOSE

WEEKS ON STUDY	05 5	06 4	08 0	08 3	08 3	08 5	08 9	09 0	09 4	09 4	09 6	09 9	10 2	10 2	10 3	10 3	10 4	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5
CARCASS ID	55 5	53 1	52 1	51 1	53 5	54 5	52 4	57 2	53 2	54 2	55 2	55 3	53 3	54 1	52 2	59 3	57 5	51 3	51 5	53 4	55 4	56 4	56 5	57 1	58 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Intestine small, jejunum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X	X			X	X		X			X				X		
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Tongue	+																								
Squamous cell carcinoma	X																								
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X	X			X	X		X									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear						X							X	X		X									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X							X	X		X									
Pheochromocytoma benign								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X					X		X									
Pars distalis, adenoma		X		X	X		X		X	X	X	X						X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X						X				X		X				X	
Follicular cell, adenoma										X															
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X							X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X		X									
Oviduct							+	+			+			+			+	+	+		+	+		+	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp																									
Polyp stromal																X			X				X		
Polyp stromal, multiple																	X								

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	591	594	603	512	523	544	563	573	574	592	601	602	514	525	543	551	561	562	581	582	583	584	595	604	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X	X	X			X			X						X	14
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Tongue																										1
Squamous cell carcinoma																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Leukemia mononuclear																										4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Pheochromocytoma benign																									X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X	X																		2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	42
Adenoma										X																1
Pituitary gland	●	+	+	+	+	+	+	+	+	+	+	+	+	●	+	+	+	+	+	+	+	●	+	+	+	50
Leukemia mononuclear																										4
Pars distalis, adenoma									X							X	X					X		X		14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma													X				X									7
Follicular cell, adenoma																							X			2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X	X					4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Oviduct	+		+	+		+	+		+	+		+		+	+	+	+	+		+	+				●	26
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp													X													1
Polyp stromal									X						X						X					6
Polyp stromal, multiple							X																			2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	055	064	080	083	083	085	089	090	094	094	096	099	102	102	103	103	104	105	105	105	105	105	105	105	105	105
CARCASS ID	555	531	521	511	535	545	524	572	532	542	552	553	533	541	522	593	575	513	515	534	554	564	565	571	585	
HEMATOPOIETIC SYSTEM																										
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear													X	X		X										
Vertebral, leukemia mononuclear						X							X	X		X										
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear																X										
Mandibular, leukemia mononuclear						X			X	X			X	X		X										
Mediastinal, leukemia mononuclear						X			X	X			X	X		X										
Pancreatic, leukemia mononuclear														X												
Renal, leukemia mononuclear									X							X										
Lymph node, mesenteric	M	M	M	M	M	+	M	M	+	+	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M
Leukemia mononuclear						X			X	X						X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X	X			X	X		X			X	X			X			
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																	
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Fibroadenoma		X														X			X	X	X		X			
Fibroadenoma, multiple																										
Leukemia mononuclear																X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										
Leukemia mononuclear						X			X	X			X	X		X			X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																										
Ear																										
Eye								+						+		+						+				
Harderian gland				+	+	+	+	+		+	+					+	+					+				
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X	X			X	X		X			X							
Ureter		+	+	+		+							+					+	+	+	+	+			+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	591	594	603	512	523	544	563	573	574	592	601	602	514	525	543	551	561	562	581	582	583	584	595	604	605	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood			+																							1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										3
Vertebral, leukemia mononuclear																										4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																										1
Mandibular, leukemia mononuclear																			X							7
Mediastinal, leukemia mononuclear																			X							7
Pancreatic, leukemia mononuclear																										1
Renal, leukemia mononuclear																										2
Lymph node, mesenteric	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M		6
Leukemia mononuclear																			X							5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear											X	X	X			X			X					X		15
Thymus	+	+	+	+	+	M	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+		41
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenocarcinoma								X																		1
Fibroadenoma			X			X						X			X	X					X	X				13
Fibroadenoma, multiple	X	X						X																	X	4
Leukemia mononuclear																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Sebaceous gland, adenoma		X																								1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Peripheral nerve	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+		45
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar carcinoma										X																1
Leukemia mononuclear													X						X					X		10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SPECIAL SENSES SYSTEM																										
Ear		+																								1
Eye			+																		+					6
Harderian gland																		+								11
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear													X						X							9
Ureter	+	+											+						+				+	+		17
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	6 mg/kg	12 mg/kg
Adrenal Cortex: Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	8.6%	4.0%	3.0%
Terminal Rates (c)	3/35 (9%)	0/22 (0%)	1/33 (3%)
Day of First Observation	731	711	731
Life Table Tests (d)	P=0.229N	P=0.475N	P=0.326N
Logistic Regression Tests (d)	P=0.227N	P=0.424N	P=0.326N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Clitoral Gland: Adenoma			
Overall Rates (a)	2/45 (4%)	(e) 2/17 (12%)	4/50 (8%)
Adjusted Rates (b)	6.3%		11.8%
Terminal Rates (c)	2/32 (6%)		3/33 (9%)
Day of First Observation	731		726
Life Table Test (d)			P=0.347
Logistic Regression Test (d)			P=0.358
Fisher Exact Test (d)			P=0.390
Mammary Gland: Fibroadenoma			
Overall Rates (a)	19/50 (38%)	9/50 (18%)	17/50 (34%)
Adjusted Rates (b)	46.7%	26.6%	48.1%
Terminal Rates (c)	14/35 (40%)	2/22 (9%)	15/33 (45%)
Day of First Observation	529	443	443
Life Table Tests (d)	P=0.447N	P=0.217N	P=0.495N
Logistic Regression Tests (d)	P=0.381N	P=0.027N	P=0.432N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.022N	P=0.418N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	19/50 (38%)	10/50 (20%)	17/50 (34%)
Adjusted Rates (b)	46.7%	29.4%	48.1%
Terminal Rates (c)	14/35 (40%)	2/22 (9%)	15/33 (45%)
Day of First Observation	529	443	443
Life Table Tests (d)	P=0.450N	P=0.303N	P=0.495N
Logistic Regression Tests (d)	P=0.382N	P=0.048N	P=0.432N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.038N	P=0.418N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	19/49 (39%)	(e) 19/40 (48%)	14/50 (28%)
Adjusted Rates (b)	43.4%		32.1%
Terminal Rates (c)	11/35 (31%)		6/33 (18%)
Day of First Observation	529		443
Life Table Test (d)			P=0.275N
Logistic Regression Test (d)			P=0.167N
Fisher Exact Test (d)			P=0.178N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	11/50 (22%)	(e) 2/17 (12%)	7/50 (14%)
Adjusted Rates (b)	30.2%		19.4%
Terminal Rates (c)	10/35 (29%)		5/33 (15%)
Day of First Observation	639		625
Life Table Test (d)			P=0.258N
Logistic Regression Test (d)			P=0.236N
Fisher Exact Test (d)			P=0.218N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	6 mg/kg	12 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	(e) 2/17 (12%)	7/50 (14%)
Adjusted Rates (b)	33.0%		19.4%
Terminal Rates (c)	11/35 (31%)		5/33 (15%)
Day of First Observation	639		625
Life Table Test (d)			P=0.188N
Logistic Regression Test (d)			P=0.170N
Fisher Exact Test (d)			P=0.154N
Uterus: Stromal Polyp			
Overall Rates (a)	8/50 (16%)	(e,f) 2/19 (11%)	9/50 (18%)
Adjusted Rates (b)	20.3%		25.7%
Terminal Rates (c)	5/35 (14%)		7/33 (21%)
Day of First Observation	656		715
Life Table Test (d)			P=0.449
Logistic Regression Test (d)			P=0.466
Fisher Exact Test (d)			P=0.500
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	14/50 (28%)	(e,g) 11/50 (22%)	15/50 (30%)
Adjusted Rates (b)	35.2%		37.6%
Terminal Rates (c)	10/35 (29%)		9/33 (27%)
Day of First Observation	676		595
Life Table Test (d)			P=0.437
Logistic Regression Test (d)			P=0.477
Fisher Exact Test (d)			P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) Three stromal sarcomas were also observed.
(g) Twenty-one livers and 22 spleens were examined microscopically.

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(16)	(50)
Foreign body		1 (6%)	1 (2%)
Inflammation, chronic active		1 (6%)	
Inflammation, suppurative			1 (2%)
Intestine large, cecum	(48)	(14)	(48)
Parasite metazoan		1 (7%)	
Intestine large, colon	(48)	(16)	(49)
Parasite metazoan	1 (2%)		4 (8%)
Intestine large, rectum	(46)	(16)	(46)
Parasite metazoan	3 (7%)	1 (6%)	1 (2%)
Intestine small, duodenum	(49)	(16)	(50)
Diverticulum	1 (2%)		
Liver	(50)	(21)	(50)
Angiectasis			1 (2%)
Basophilic focus	40 (80%)	7 (33%)	37 (74%)
Clear cell focus	1 (2%)		
Degeneration, cystic			2 (4%)
Hepatodiaphragmatic nodule	6 (12%)	2 (10%)	5 (10%)
Inflammation, chronic	27 (54%)	7 (33%)	29 (58%)
Inflammation, necrotizing	4 (8%)		
Necrosis, coagulative	1 (2%)		2 (4%)
Vacuolization cytoplasmic	2 (4%)	1 (5%)	
Portal vein, necrosis, fibrinoid	1 (2%)		
Portal vein, intima, proliferation	1 (2%)		
Mesentery	(49)	(18)	(49)
Inflammation, chronic active	1 (2%)	2 (11%)	1 (2%)
Necrosis		2 (11%)	1 (2%)
Pancreas	(50)	(17)	(50)
Acinus, atrophy	6 (12%)	2 (12%)	10 (20%)
Duct, ectasia			1 (2%)
Salivary glands	(50)	(16)	(50)
Atrophy	1 (2%)		
Stomach, forestomach	(49)	(16)	(50)
Inflammation, chronic active	2 (4%)	1 (6%)	
Ulcer	1 (2%)		
Epithelium, hyperplasia			1 (2%)
Stomach, glandular	(49)	(16)	(50)
Inflammation, chronic active		2 (13%)	
Mineralization			1 (2%)
CARDIOVASCULAR SYSTEM			
Blood vessel	(50)	(16)	(47)
Pulmonary artery, mineralization	1 (2%)		
Heart	(50)	(16)	(50)
Cardiomyopathy, chronic	47 (94%)	7 (44%)	48 (96%)
Inflammation, chronic active			1 (2%)
Mineralization			1 (2%)
Atrium, thrombus		1 (6%)	1 (2%)
Valve, bacterium		1 (6%)	1 (2%)
Valve, inflammation, chronic active		1 (6%)	
Valve, thrombus		1 (6%)	1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		1 (2%)
Capsule, inflammation, chronic		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)
Cyst	1 (2%)		
Degeneration, fatty	10 (20%)	17 (34%)	16 (32%)
Hyperplasia	13 (26%)	16 (32%)	18 (36%)
Hypertrophy	2 (4%)	5 (10%)	8 (16%)
Infiltration cellular, lymphocytic		1 (2%)	
Adrenal gland, medulla	(50)	(50)	(50)
Hyperplasia	4 (8%)	5 (10%)	6 (12%)
Pituitary gland	(49)	(40)	(50)
Pars distalis, angiectasis			6 (12%)
Pars distalis, cyst	14 (29%)	10 (25%)	25 (50%)
Pars distalis, hyperplasia	11 (22%)	11 (28%)	12 (24%)
Pars intermedia, hyperplasia			1 (2%)
Thyroid gland	(50)	(17)	(50)
C-cell, hyperplasia	20 (40%)	3 (18%)	14 (28%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(45)	(17)	(50)
Hyperplasia	1 (2%)		1 (2%)
Inflammation, chronic active	2 (4%)	1 (6%)	1 (2%)
Duct, dilatation	1 (2%)		
Ovary	(50)	(20)	(50)
Cyst	4 (8%)	4 (20%)	3 (6%)
Uterus	(50)	(19)	(50)
Dilatation	6 (12%)		6 (12%)
Diverticulum		1 (5%)	1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic active	1 (2%)	2 (11%)	
Cervix, fibrosis			1 (2%)
Endometrium, hyperplasia, cystic, glandular	8 (16%)	1 (5%)	14 (28%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(16)	(50)
Femoral, hyperplasia			1 (2%)
Femoral, hyperplasia, reticulum cell	5 (10%)	3 (19%)	3 (6%)
Femoral, myelofibrosis		1 (6%)	1 (2%)
Femoral, myeloid cell, hyperplasia		1 (6%)	
Vertebral, hyperplasia			1 (2%)
Lymph node	(50)	(21)	(50)
Mandibular, hyperplasia, plasma cell		1 (5%)	1 (2%)
Mandibular, pigmentation, hemosiderin			1 (2%)
Mediastinal, inflammation, necrotizing		1 (5%)	
Mediastinal, pigmentation, hemosiderin	37 (74%)		37 (74%)
Pancreatic, pigmentation, hemosiderin	1 (2%)		
Spleen	(50)	(22)	(50)
Fibrosis		1 (5%)	
Hematopoietic cell proliferation	26 (52%)	2 (9%)	32 (64%)
Pigmentation, hemosiderin	31 (62%)		32 (64%)
Thrombus		1 (5%)	
Thymus	(38)	(16)	(41)
Cyst	2 (5%)		4 (10%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	(24)	(50)
Hyperplasia, cystic	48 (98%)	18 (75%)	48 (96%)
Skin	(50)	(24)	(50)
Inflammation, chronic active			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(16)	(50)
Femur, fibrous osteodystrophy			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(16)	(50)
Compression	14 (28%)	4 (25%)	13 (26%)
Hydrocephalus		2 (13%)	2 (4%)
Inflammation, chronic active		1 (6%)	
Spinal cord	(50)	(16)	(50)
White matter, degeneration	18 (36%)		11 (22%)
RESPIRATORY SYSTEM			
Lung	(50)	(17)	(50)
Granuloma		7 (41%)	5 (10%)
Inflammation, chronic active	1 (2%)		1 (2%)
Pigmentation, hemosiderin		1 (6%)	
Alveolar epithelium, hyperplasia	1 (2%)		3 (6%)
Nose	(50)	(16)	(50)
Inflammation, chronic active	3 (6%)		1 (2%)
Nasolacrimal duct, granuloma			1 (2%)
Nasolacrimal duct, inflammation, chronic	20 (40%)		20 (40%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)		2 (4%)
SPECIAL SENSES SYSTEM			
Eye	(5)	(5)	(6)
Lens, cataract	2 (40%)	2 (40%)	5 (83%)
Retina, atrophy	2 (40%)	1 (20%)	3 (50%)
URINARY SYSTEM			
Kidney	(50)	(17)	(50)
Bacterium		1 (6%)	1 (2%)
Calculus micro observation only	2 (4%)		
Hydronephrosis	2 (4%)		
Infarct		1 (6%)	
Inflammation, chronic active	2 (4%)	1 (6%)	1 (2%)
Mineralization			1 (2%)
Nephropathy, chronic	48 (96%)	11 (65%)	44 (88%)
Pigmentation, hemosiderin		1 (6%)	
Renal tubule, atrophy	1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)		
Urinary bladder	(50)	(14)	(50)
Calculus micro observation only	1 (2%)		
Dilatation		1 (7%)	
Inflammation, chronic active		1 (7%)	
Transitional epithelium, hyperplasia	2 (4%)	1 (7%)	

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	*(50)	(48)
Lymphoma malignant histiocytic	1 (2%)		
Gallbladder	(44)	*(50)	(33)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)
Intestine small, duodenum	(45)	*(50)	(40)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)
Polyp adenomatous	1 (2%)		
Intestine small, jejunum	(45)	*(50)	(40)
Adenocarcinoma		1 (2%)	
Lymphoma malignant histiocytic		1 (2%)	
Liver	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Hemangiosarcoma		2 (4%)	
Hepatocellular carcinoma	3 (6%)	7 (14%)	10 (20%)
Hepatocellular carcinoma, multiple	3 (6%)	6 (12%)	2 (4%)
Hepatocellular adenoma	3 (6%)	3 (6%)	13 (26%)
Hepatocellular adenoma, multiple	5 (10%)	1 (2%)	6 (12%)
Lymphoma malignant histiocytic	4 (8%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Adenocarcinoma, metastatic, stomach		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant histiocytic	2 (4%)	1 (2%)	
Lymphoma malignant lymphocytic			3 (6%)
Pancreas	(49)	*(50)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Salivary glands	(49)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Stomach, forestomach	(50)	(49)	(48)
Mast cell tumor benign	1 (2%)		
Papilloma squamous		1 (2%)	2 (4%)
Stomach, glandular	(50)	(20)	(45)
Adenocarcinoma		1 (5%)	
Lymphoma malignant histiocytic		1 (5%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Adenocarcinoma, metastatic, stomach		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic, lung			2 (4%)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(48)	*(50)	(48)
Capsule, adenoma	1 (2%)		
Capsule, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Adrenal gland, medulla	(48)	*(50)	(50)
Pheochromocytoma benign	1 (2%)	1 (2%)	2 (4%)
Bilateral, pheochromocytoma benign	1 (2%)		1 (2%)
Islets, pancreatic	(50)	*(50)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Pituitary gland	(48)	*(50)	(42)
Pars distalis, adenoma		1 (2%)	
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	*(50)	(49)
Follicular cell, adenoma		1 (2%)	2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ductus deferens	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic			1 (2%)
Epididymis	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Prostate	(49)	*(50)	(50)
Lymphoma malignant lymphocytic			2 (4%)
Seminal vesicle	*(50)	*(50)	*(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Testes	(50)	*(50)	(50)
Adenocarcinoma, metastatic, stomach		1 (2%)	
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
Bone marrow	(50)	*(50)	(50)
Femoral, adenocarcinoma, metastatic, stomach		1 (2%)	
Femoral, lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Femoral, lymphoma malignant lymphocytic			2 (4%)
Vertebral, lymphoma malignant histiocytic	1 (2%)		
Vertebral, lymphoma malignant lymphocytic			1 (2%)
Lymph node	(49)	*(50)	(50)
Axillary, fibrosarcoma, metastatic, skin			1 (2%)
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Inguinal, lymphoma malignant lymphocytic			1 (2%)
Lumbar, lymphoma malignant lymphocytic	1 (2%)		
Lumbar, lymphoma malignant mixed		1 (2%)	
Mandibular, lymphoma malignant histiocytic	2 (4%)	1 (2%)	
Mandibular, lymphoma malignant lymphocytic	1 (2%)		
Mandibular, lymphoma malignant mixed		1 (2%)	2 (4%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Mediastinal, lymphoma malignant histiocytic	2 (4%)	2 (4%)	1 (2%)
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		2 (4%)
Mediastinal, lymphoma malignant mixed			1 (2%)
Mediastinal, mandibular, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Pancreatic, lymphoma malignant histiocytic	1 (2%)		
Renal, lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Renal, lymphoma malignant mixed		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mesenteric	(19)	*(50)	(24)
Lymphoma malignant histiocytic	3 (16%)	3 (6%)	
Lymphoma malignant lymphocytic	1 (5%)		2 (8%)
Lymphoma malignant mixed		3 (6%)	2 (8%)
Mediastinal, adenocarcinoma, metastatic, stomach		1 (2%)	
Spleen	(50)	*(50)	(50)
Hemangiosarcoma			2 (4%)
Lymphoma malignant histiocytic	5 (10%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		3 (6%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed		1 (2%)	2 (4%)
Thymus	(36)	*(50)	(39)
Alveolar/bronchiolar carcinoma, metastatic, lung			3 (8%)
Lymphoma malignant histiocytic	1 (3%)		
Lymphoma malignant lymphocytic	1 (3%)		4 (10%)
Lymphoma malignant mixed			1 (3%)
INTEGUMENTARY SYSTEM			
Skin	(50)	*(50)	(50)
Adenocarcinoma, metastatic, stomach		1 (2%)	
Basal cell adenoma			1 (2%)
Subcutaneous tissue, fibroma	4 (8%)		3 (6%)
Subcutaneous tissue, fibrosarcoma	13 (26%)	14 (28%)	10 (20%)
Subcutaneous tissue, fibrosarcoma, multiple	2 (4%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)
Skeletal muscle	*(50)	*(50)	*(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Fibrosarcoma, metastatic, skin	3 (6%)	7 (14%)	3 (6%)
Lymphoma malignant lymphocytic			2 (4%)
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic			1 (2%)
Meningioma benign		1 (2%)	
Spinal cord	(48)	*(50)	(49)
Lymphoma malignant histiocytic	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(49)	(50)	(50)
Adenocarcinoma, metastatic, stomach		1 (2%)	
Alveolar/bronchiolar adenoma	3 (6%)	6 (12%)	10 (20%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	9 (18%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung (Continued)	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	2 (4%)	1 (2%)
Lymphoma malignant histiocytic	3 (6%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		2 (4%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed		1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			2 (4%)
Mediastinum, lymphoma malignant histiocytic	1 (2%)		
Nose	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	(48)	(49)	(50)
Adenoma	1 (2%)	13 (27%)	27 (54%)
Carcinoma	1 (2%)		2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		
Bilateral, adenoma		1 (2%)	2 (4%)
URINARY SYSTEM			
Kidney	(50)	*(50)	(50)
Adenocarcinoma, metastatic, stomach		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic, lung			2 (4%)
Fibrosarcoma, metastatic, skin	1 (2%)		
Lymphoma malignant histiocytic	3 (6%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic	2 (4%)		4 (8%)
Lymphoma malignant mixed			2 (4%)
Urethra	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
Urinary bladder	(49)	*(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	2 (4%)		4 (8%)
Lymphoma malignant histiocytic	6 (12%)	3 (6%)	2 (4%)
Hemangiosarcoma		2 (4%)	2 (4%)
Lymphoma malignant mixed		3 (6%)	2 (4%)
Lymphoma malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	29	20	20
Moribund	12	14	11
Dead	9	16	19

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	35	39	47
Total primary neoplasms	54	71	116
Total animals with benign neoplasms	16	22	38
Total benign neoplasms	22	29	70
Total animals with malignant neoplasms	28	33	35
Total malignant neoplasms	32	42	46
Total animals with secondary neoplasms ***	5	10	9
Total secondary neoplasms	6	18	33

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: VEHICLE CONTROL

WEEKS ON STUDY	01 5	02 6	02 9	03 2	04 3	06 2	06 7	06 7	07 6	08 5	08 9	09 0	09 2	09 5	09 7	09 7	09 8	09 8	09 8	10 5	10 5	10 5	10 5	10 5
CARCASS ID	04 5	07 5	09 5	04 4	06 5	10 5	07 1	04 3	03 5	07 4	04 2	03 3	08 5	02 1	07 3	08 1	05 3	10 2	03 2	04 1	01 5	03 1	03 4	06 2	06 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																	X								
Gallbladder	+	A	+	+	+	+	A	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, rectum	+	M	+	+	+	+	A	A	+	+	+	+	A	+	+	+	M	+	+	M	+	+	+	+	+
Intestine small	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	+	M	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																				X					
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																								X	X
Lymphoma malignant histiocytic						X				X			X				X								
Mesentery	+		+	+	+			+	+	+	+			+	+	+	+	+	+		+	+	+		+
Lymphoma malignant histiocytic										X							X								
Pancreas	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor benign																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X			X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Capsule, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																	X								
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	M	+	+	+	+	+	M	+	M	+	M	+	+	M	+	M	M	M	M	+
Pituitary gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Coagulating gland	+	+		+				+	+	+	+		+		+	+	+		+					+	+
Ductus deferens	+	+			+			+	+	+	+		+	+	+		+		+					+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis			+															+			+				
Preputial gland				+																					
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle		+	+		+			+	+	+	+		+	+	+	+	+		+	+					+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
: Present but not examined microscopically
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	0082	0111	0112	0113	0114	0123	0124	0255	0051	0554	0555	0561	0583	0584	0594	0101	0222	0552	0664	0772	0991	0992	0993	1003	1004	TOTAL: TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Polyp adenomatous																						X				1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma											X										X					3
Hepatocellular carcinoma, multiple															X	X			X							3
Hepatocellular adenoma	X																	X			X					3
Hepatocellular adenoma, multiple								X		X									X							5
Lymphoma malignant histiocytic																										4
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant histiocytic																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor benign							X																			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	48
Capsule, adenoma		X																								1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+	48
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	M	M	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
Tissue, NOS													M													
GENITAL SYSTEM																										
Coagulating gland	+			+		+		+	+				+	+					+	+		+		+	+	26
Ductus deferens	+			+		+					+		+			+	+			+			+			23
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										3
Preputial gland										+			+													3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+			+		+		+	+		+		+	+	+		+		+		+			+	+	29
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	015	026	029	032	043	062	067	067	076	085	089	090	092	095	097	097	098	098	098	105	105	105	105	105
CARCASS ID	045	075	095	044	065	105	071	043	035	074	042	033	085	021	073	081	053	102	032	041	015	031	034	062	063
HEMATOPOIETIC SYSTEM																									
Blood				+					+	+															
Lymphoma malignant lymphocytic									X																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, lymphoma malignant histiocytic													X												
Vertebral, lymphoma malignant histiocytic						X																			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant lymphocytic									X																
Mandibular, lymphoma malignant histiocytic										X			X												
Mandibular, lymphoma malignant lymphocytic									X																
Mediastinal, lymphoma malignant histiocytic													X				X								
Mediastinal, lymphoma malignant lymphocytic									X																
Pancreatic, lymphoma malignant histiocytic										X															
Renal, lymphoma malignant lymphocytic									X																
Lymph node, mesenteric	M	M	M	M	M	M	M	M	+	+	+	+	+	+	M	M	+	M	M	M	+	+	M	M	+
Lymphoma malignant histiocytic										X			X				X								
Lymphoma malignant lymphocytic									X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X			X				X								
Lymphoma malignant lymphocytic									X																
Thymus	+	M	+	+	+	M	M	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																	X								
Lymphoma malignant lymphocytic									X																
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma							X							X	X			X	X			X			
Subcutaneous tissue, fibrosarcoma, multiple											X	X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin											X	X							X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X			X												
Peripheral nerve	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
RESPIRATORY SYSTEM																									
Larynx																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																X									
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant histiocytic										X			X				X								
Lymphoma malignant lymphocytic									X																
Mediastinum, lymphoma malignant histiocytic																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye			+																						
Harderian gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Lymphoma malignant lymphocytic									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin												X													
Lymphoma malignant histiocytic										X			X				X								
Lymphoma malignant lymphocytic									X									X							
Ureter	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+		+	+	+	
Urethra		+	+	+	+	+	+		+	+				+	+	+		+			+	+	+		
Lymphoma malignant lymphocytic									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0821	0111	0112	0113	0114	0123	0124	0125	0551	0554	0555	0561	0583	0584	0594	1011	0222	0552	0564	0772	0791	0992	0993	1003	1004	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										3
Lymphoma malignant lymphocytic																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, lymphoma malignant histiocytic																										1
Vertebral, lymphoma malignant histiocytic																										1
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lumbar, lymphoma malig. lymphocytic																										1
Mandibular, lymphoma malignant histiocytic																										2
Mandibular, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant histiocytic																										1
Renal, lymphoma malig. lymphocytic																										1
Lymph node, mesenteric	+	M	M	M	M	M	M	M	+	M	M	M	M	+	M	M	+	M	+	M	+	+	M	+	+	19
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic									X						X											5
Lymphoma malignant lymphocytic																										1
Thymus	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	M	M	+	+	M	+	+	+	+	36
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma			X							X				X							X					4
Subcutaneous tissue, fibrosarcoma	X	X	X							X						X	X	X								13
Subcutaneous tissue, fibrosarcoma, multiple																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
RESPIRATORY SYSTEM																										
Larynx		+																								1
Lung	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X						X																		3
Alveolar/bronchiolar carcinoma				X																						2
Hepatocellular carcinoma, metastatic, liver											X										X					2
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic																										1
Mediastinum, lymphoma malignant histiocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																				X						1
Carcinoma															X											1
Lymphoma malignant lymphocytic																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic																										2
Ureter	+	+	+	+	+	+		+				+	+		+	+	+	+	+	+	+		+	+		39
Urethra		+	+		+			+	+			+	+	+		+	+		+	+	+		+	+		30
Lymphoma malignant lymphocytic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Lymphoma malignant lymphocytic																										1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: LOW DOSE

WEEKS ON STUDY	00 08	01 16	01 17	01 18	02 20	02 24	02 29	03 32	06 00	06 02	06 05	06 66	07 00	07 22	07 22	08 86	08 88	08 89	09 01	09 11	09 44	09 98	09 98	09 98	09 99
CARCASS ID	22 21	21 15	21 14	22 25	21 13	23 32	22 24	27 75	24 43	27 74	29 92	25 51	26 64	30 03	24 41	23 33	25 52	26 65	29 95	30 05	27 71	26 61	26 62	23 35	21 12
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Gallbladder	+	+	M	A	A	+	+	A	A	+	+	A	M	+	+	+	A	+	+	+					
Intestine large	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+					
Intestine large, cecum	+	+	+	+	+	+	+	M	A	+	+	+	A	+	+	+	A	A	+	+					
Intestine large, colon	M	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+					
Intestine large, rectum	M	+	M	+	M	+	A	A	A	+	+	+	A	M	+	+	A	+	+	+					
Intestine small	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	A	+	+	+					
Intestine small, duodenum	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	A	+	+	+					
Intestine small, ileum	+	+	+	+	A	+	+	A	A	+	+	+	A	+	+	+	A	A	+	+					
Intestine small, jejunum	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	A	M	+	+					
Adenocarcinoma																									
Lymphoma malignant histiocytic																X									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																						X			
Hepatocellular carcinoma, multiple											X						X						X	X	
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic														X		X									
Mesentery	+	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+					
Adenocarcinoma, metastatic, stomach																		X							
Lymphoma malignant histiocytic														X											
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+					+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Papilloma squamous																			X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+					
Adenocarcinoma																		X							
Lymphoma malignant histiocytic																X									
Tongue				M																					
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Adenocarcinoma, metastatic, stomach																		X							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+			+		
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+					
Parathyroid gland	M	+	M	M	+	+	M	M	I	+	M	+	+	+	+	+	+	M	+	+					
Pituitary gland	+	+	+	+	+	M	+	M	M	+	+	+	I	+	+	M	+	+	M	M					
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Follicular cell, adenoma																		X							
GENERAL BODY SYSTEM																									
Tissue, NOS								+																	
GENITAL SYSTEM																									
Coagulating gland		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+					
Ductus deferens	+	+	+	+	+	+	+	+	+			+	+	+	+		+	+		+					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Penis					+		+																		
Preputial gland	+	+	+	+	+	+	+	+														+			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Seminal vesicle	M	+	M	+	+	+	+	+	+		+	+		+	+	M	+	+	+	+					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Adenocarcinoma, metastatic, stomach																		X							

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	099	099	102	102	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	263	285	211	291	234	222	242	444	254	272	282	283	293	302	304	223	231	273	281	301	245	253	255	284	294	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										20
Gallbladder																										12
Intestine large																										17
Intestine large, cecum																										15
Intestine large, colon																										16
Intestine large, rectum																										11
Intestine small												+														17
Intestine small, duodenum																										16
Intestine small, ileum																										14
Intestine small, jejunum												+														16
Adenocarcinoma												X														1
Lymphoma malignant histiocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X													X					2
Hepatocellular carcinoma							X				X	X					X						X	X		7
Hepatocellular carcinoma, multiple			X	X																						6
Hepatocellular adenoma		X												X					X							3
Hepatocellular adenoma, multiple																X										1
Lymphoma malignant histiocytic																										2
Mesentery																										18
Adenocarcinoma, metastatic, stomach																										1
Lymphoma malignant histiocytic																										1
Pancreas				+																						21
Salivary glands																										20
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																										1
Stomach, glandular													+													20
Adenocarcinoma																										1
Lymphoma malignant histiocytic																										1
Tongue																										
Tooth																										20
CARDIOVASCULAR SYSTEM																										
Blood vessel																										19
Heart																										20
Adenocarcinoma, metastatic, stomach																										1
ENDOCRINE SYSTEM																										
Adrenal gland																										21
Adrenal gland, cortex																										21
Adrenal gland, medulla																										20
Pheochromocytoma benign																										1
Islets, pancreatic																										19
Parathyroid gland																										12
Pituitary gland															+											14
Pars distalis, adenoma															X											1
Thyroid gland																										20
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Coagulating gland																										18
Ductus deferens																										16
Epididymis																										20
Penis																										2
Preputial gland																										9
Prostate																										20
Seminal vesicle						+									+	+										18
Testes																										20
Adenocarcinoma, metastatic, stomach																										1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	008	016	017	018	020	024	029	032	060	062	065	066	070	072	072	086	088	089	091	091	094	098	098	098	099
CARCASS ID	221	215	144	225	213	232	224	275	243	274	292	251	264	303	241	233	252	265	295	305	271	261	262	235	212
HEMATOPOIETIC SYSTEM																									
Blood										+									+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Femoral, adenocarcinoma, metastatic, stomach																		X							
Femoral, lymphoma malignant histiocytic																X									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Lumbar, lymphoma malignant mixed																									
Mandibular, lymphoma malignant histiocytic														X											
Mandibular, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant histiocytic														X		X									
Renal, lymphoma malignant mixed																									
Lymph node, mesenteric	M	M	M	A	M	M	M	M	M	+	M	M	M	+	M	+	M	+	+	+					
Lymphoma malignant histiocytic														X		X									
Lymphoma malignant mixed																									
Mediastinal, adenocarcinoma, metastatic, stomach																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Lymphoma malignant histiocytic														X											
Lymphoma malignant mixed																									
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	M	M	+	+	M	M	+	M					
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenocarcinoma, metastatic, stomach																		X							
Subcutaneous tissue, fibrosarcoma										X	X								X	X	X	X	X		
Subcutaneous tissue, fibrosarcoma, multiple																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Fibrosarcoma, metastatic, skin										X									X	X	X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Meningioma benign															X										
Peripheral nerve	+	M	M	+	+	M	+	+	+	M	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, stomach																		X							
Alveolar/bronchiolar adenoma																X		X		X					
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									X
Fibrosarcoma, metastatic, skin																					X				
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant histiocytic														X		X									
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
SPECIAL SENSES SYSTEM																									
Ear																		+							
Eye																									
Harderian gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X					X							
Bilateral, adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Adenocarcinoma, metastatic, stomach																		X							
Lymphoma malignant histiocytic														X		X									
Ureter	+	+		+	+	+				+	+	+	+	+	+	+		+	+	+					
Urethra	+	+	+		+		+	+				+				+									
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+			+		

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	099	099	102	102	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	263	285	211	291	234	222	242	244	254	272	282	283	293	302	304	223	231	273	281	301	245	253	255	284	294	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Bone marrow																										20
Femoral, adenocarcinoma, metastatic, stomach																										1
Femoral, lymphoma malignant histiocytic																										1
Lymph node	+				+	+		+		+	+						+		+		+	+	+	+		32
Lumbar, lymphoma malignant mixed																								X		1
Mandibular, lymphoma mal. histiocytic																										1
Mandibular, lymphoma malignant mixed																						X				1
Mediastinal, lymphoma malignant histiocytic																										2
Renal, lymphoma malignant mixed																								X		1
Lymph node, mesenteric					+	+		+		+	+						+		+		+	+	+	+		17
Lymphoma malignant histiocytic																	X									3
Lymphoma malignant mixed																			X			X		X		3
Mediastinal, adenocarcinoma, metastatic, stomach																										1
Spleen	+				+							+					+					+		+		26
Lymphoma malignant histiocytic																	X									2
Lymphoma malignant mixed																								X		1
Thymus																										13
INTEGUMENTARY SYSTEM																										
Mammary gland																										
Skin	+	+		+	+					+			+		+				+			+		+		33
Adenocarcinoma, metastatic, stomach																										1
Subcutaneous tissue, fibrosarcoma	X	X		X	X					X			X											X		14
Subcutaneous tissue, fibrosarcoma, multiple															X											1
MUSCULOSKELETAL SYSTEM																										
Bone					+			+	+	+	+	+	+			+	+	+	+		+				+	34
Skeletal muscle		+								+														+		24
Fibrosarcoma, metastatic, skin		X								X														X		7
NERVOUS SYSTEM																										
Brain																										20
Meningioma benign																										1
Peripheral nerve	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	39
Spinal cord																										20
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, stomach																										1
Alveolar/bronchiolar adenoma				X													X							X		6
Alveolar/bronchiolar carcinoma						X		X	X																	3
Alveolar/bronchiolar carcinoma, multiple																										1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver			X																				X			2
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed																						X				1
Nose																										20
Trachea																										20
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye		+								+																2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X		X	X						X		X			X		X			X	X		X	X	13
Bilateral, adenoma											X															1
URINARY SYSTEM																										
Kidney				+																				+		22
Adenocarcinoma, metastatic, stomach																										1
Lymphoma malignant histiocytic																										2
Ureter																										15
Urethra																										8
Urinary bladder																							+			21

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: HIGH DOSE

WEEKS ON STUDY	026	037	053	064	068	068	069	070	070	072	072	076	079	082	084	085	090	093	093	093	094	096	096	096	099
CARCASS ID	461	485	515	511	441	848	244	711	555	221	255	50	435	535	442	655	522	512	663	622	431	445	955	933	883
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	A	+	A	A	A	A	+	M	M	A	A	A	+	A	+	+	+	A	+	+	+	A
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Intestine large	+	+	+	+	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	A	A	A	+	M	A	A	+	+		+	A	A	A	+	+	+	+	+	+	+	+		+
Intestine large, colon	+	+	+	+	+	+	A	A	+	+		+	A	A	+	+	+	+	+	+	+	+	+		+
Intestine large, rectum	M	+	+	+	+	+	A	A	+	+		+	A	A	+	+	+	+	+	+	+	+	+		+
Intestine small	A	A	+	+	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	+	+	A	A	+	+		+	A	A	+	+	+	+	+	+	+	+	+		+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Intestine small, ileum	A	A	A	A	+	+	A	A	+	+		+	A	A	+	+	+	+	+	+	+	+	+		+
Intestine small, jejunum	A	A	A	+	+	+	A	A	+	+		+	A	A	+	+	+	+	+	+	+	+	+		+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Hepatocellular carcinoma												X	X		X						X	X			
Hepatocellular carcinoma, multiple											X												X		
Hepatocellular adenoma			X	X														X				X			
Hepatocellular adenoma, multiple																								X	
Lymphoma malignant histiocytic															X										
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant							X																		
Mesentery	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Lymphoma malignant lymphocytic		X																							
Pancreas	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Lymphoma malignant lymphocytic																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Stomach	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								X	
Stomach, glandular	+	A	+	A	+	+	A	+	+	+		+	A	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel			+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+		+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X	X					
Lymphoma malignant lymphocytic		X																							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Parathyroid gland	+	+	M	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	M	+
Pituitary gland	+	M	+	M	+	M	A	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Coagulating gland	+	+		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Ductus deferens	+	+	+		+		+	+	+	+			+	+	+	+	+	+		+	+				
Lymphoma malignant lymphocytic		X																							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Penis	+							+																+	
Preputial gland							+	+			+												+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Seminal vesicle		+		+			+	+	+	+	+		+		+	+	+	+	+			+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	0 9 9	0 9 9	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	4 2 3	4 3 3	4 1 3	4 7 3	4 1 4	4 3 4	4 6 4	4 7 2	4 7 5	4 8 2	5 0 5	4 7 4	4 8 1	4 9 1	4 9 4	5 0 3	4 2 2	4 3 2	4 4 3	4 4 4	4 5 1	4 5 4	4 9 2	5 0 2	5 0 4	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		48
Gallbladder	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		33
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		37
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		42
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		40
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Intestine small, ileum	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	+	+		37
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocellular carcinoma							X			X	X		X	X												10
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X					X	X	X		X		X	X		X			X								13
Hepatocellular adenoma, multiple					X				X					X									X		X	6
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic									X																	2
Lymphoma malignant																										1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant lymphocytic			X						X																	3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant lymphocytic			X																							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic			X																							1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Papilloma squamous																							X			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+			+	+	+		+	+	+	+	+					+	+					+	+	34
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar carcinoma, metastatic, lung																										2
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		48
Capsule, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma benign						X								X												2
Bilateral, pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+		38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		42
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		49
Follicular cell, adenoma		X																	X							2
GENERAL BODY SYSTEM																										
Tissue, NOS				+																						1
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Ductus deferens			+	+	+	+	+		+			+	+	+	+								+	+		28
Lymphoma malignant lymphocytic																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic									X																	1
Penis																								+		4
Preputial gland									+														+			6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic			X																							2
Seminal vesicle	+		+	+	+	+		+	+			+	+		+	+	+		+	+	+		+	+	+	36
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	026	037	053	064	068	068	069	070	070	072	072	076	079	082	084	085	090	093	093	093	094	096	096	096	099
CARCASS ID	461	485	515	511	441	484	424	471	555	421	425	501	435	453	442	465	452	412	463	462	431	445	495	493	483
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, lymphoma malignant lymphocytic		X																							
Vertebral, lymphoma malignant lymphocytic																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, fibrosarcoma, metastatic, skin														X											
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																									
Inguinal, lymphoma malignant lymphocytic																									
Mandibular, lymphoma malignant mixed																									
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																				X					
Mediastinal, lymphoma malignant histiocytic															X										
Mediastinal, lymphoma malignant lymphocytic													X												
Mediastinal, lymphoma malignant mixed																									
Mediastinal, mandibular, alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Renal, lymphoma malignant lymphocytic																									
Lymph node, mesenteric	M	+	M	M	M	M	M	M	M	+	+	M	M	+	M	+	+	M	M	+	M	M	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant histiocytic															X										
Lymphoma malignant lymphocytic		X											X												
Lymphoma malignant							X																		
Lymphoma malignant mixed																									
Thymus	M	+	+	+	+	+	A	M	+	+	M	+	+	+	M	+	+	M	+	+	M	+	M	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X			X	X					
Lymphoma malignant lymphocytic		X											X												
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Subcutaneous tissue, fibroma																	X	X							
Subcutaneous tissue, fibrosarcoma								X		X				X			X	X							
Subcutaneous tissue, fibrosarcoma, multiple																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																				X					
Fibrosarcoma, metastatic, skin										X															
Lymphoma malignant lymphocytic		X																							
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Carcinoma, metastatic, harderian gland																								X	
Lymphoma malignant lymphocytic		X																							
Peripheral nerve	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	099	099	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	4233	4333	4413	4737	4114	4334	4664	4722	4755	4822	5055	4744	4881	4991	4994	5033	4222	4332	4443	4444	4551	4554	4992	5022	5044	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, lymphoma malignant lymphocytic									X																	2
Vertebral, lymphoma malignant lymphocytic									X																	1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, fibrosarcoma, metastatic, skin																										1
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																					X					1
Inguinal, lymphoma malignant lymphocytic			X																							1
Mandibular, lymphoma malig. mixed						X					X															2
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic			X																							2
Mediastinal, lymphoma malig. mixed						X																				1
Mediastinal, mandibular, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Renal, lymphoma malig. lymphocytic			X																							1
Lymph node, mesenteric	+	M	+	M	+	+	M	M	M	M	+	M	+	+	+	+	M	+	M	+	M	M	+	+	+	24
Lymphoma malignant lymphocytic			X																							2
Lymphoma malignant mixed						X					X															2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X	X																2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic			X																							3
Lymphoma malignant																										1
Lymphoma malignant mixed						X					X															2
Thymus	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	39
Alveolar/bronchiolar carcinoma, metastatic, lung																										3
Lymphoma malignant lymphocytic			X						X																	4
Lymphoma malignant mixed						X																				1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																							X			1
Subcutaneous tissue, fibroma																							X			3
Subcutaneous tissue, fibrosarcoma		X											X		X						X	X				10
Subcutaneous tissue, fibrosarcoma, multiple																X										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																X										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Fibrosarcoma, metastatic, skin																X					X					3
Lymphoma malignant lymphocytic			X																							2
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Carcinoma, metastatic, harderian gland																										1
Lymphoma malignant lymphocytic																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	43
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	026	037	053	064	068	068	069	070	070	072	072	076	079	082	084	085	090	093	093	093	094	096	096	096	099
CARCASS ID	461	485	415	411	441	484	424	471	455	421	425	501	435	453	442	465	452	412	463	462	431	445	495	493	483
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X															X		X					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																X			X	X			X		X
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, harderian gland																								X	
Fibrosarcoma, metastatic, skin																									
Hepatocellular carcinoma, metastatic, liver												X													
Lymphoma malignant histiocytic															X										
Lymphoma malignant lymphocytic		X											X												
Lymphoma malignant							X																		
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																X			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																								+	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X				X				X	X		X		X	X	X		X	X	X	X
Carcinoma																								X	
Bilateral, adenoma								X																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X	X					
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic		X											X												
Lymphoma malignant mixed																									
Ureter		+	+	+		+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+			+
Urethra	+		+		+	+			+		+			+	+		+	+	+		+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Lymphoma malignant lymphocytic																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	099	099	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	423	433	413	473	414	434	646	472	475	482	505	474	481	491	494	503	422	432	443	444	451	454	492	502	504	TOTAL: TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X	X		X			X						X					X			X			10
Alveolar/bronchiolar adenoma, multiple								X																		1
Alveolar/bronchiolar carcinoma				X				X								X					X					9
Alveolar/bronchiolar carcinoma, multiple										X																1
Carcinoma, metastatic, harderian gland																										1
Fibrosarcoma, metastatic, skin																X										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye							+					+												+		4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X	X	X	X	X	X	X	X	X		X	X						X			X		X	27
Carcinoma																									X	2
Bilateral, adenoma												X														2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										2
Lymphoma malignant histiocytic		X																								1
Lymphoma malignant lymphocytic			X						X																	4
Lymphoma malignant mixed						X					X															2
Ureter	+	+			+	+	+		+	+	+	+	+	+	+	+	+				-		+	+	+	38
Urethra	+	+	+			+	+	+	+	+	+	+	+	+	+		+	+	+	+		+		+		35
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant lymphocytic									X																	1

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	25 mg/kg	50 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	2/48 (4%)	(b) 1/21 (5%)	3/50 (6%)
Adjusted Rates (c)	6.6%		14.3%
Terminal Rates (d)	1/28 (4%)		3/21 (14%)
Day of First Observation	683		731
Life Table Test (e)			P=0.377
Logistic Regression Test (e)			P=0.424
Fisher Exact Test (e)			P=0.520
Harderian Gland: Adenoma			
Overall Rates (a)	1/48 (2%)	14/49 (29%)	29/50 (58%)
Adjusted Rates (c)	3.4%	54.8%	77.6%
Terminal Rates (d)	1/29 (3%)	9/20 (45%)	13/21 (62%)
Day of First Observation	731	485	476
Life Table Tests (e)	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (e)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (e)	P<0.001		
Fisher Exact Test (e)		P<0.001	P<0.001
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	14/49 (29%)	30/50 (60%)
Adjusted Rates (c)	6.9%	54.8%	80.4%
Terminal Rates (d)	2/29 (7%)	9/20 (45%)	14/21 (67%)
Day of First Observation	731	485	476
Life Table Tests (e)	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (e)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (e)	P<0.001		
Fisher Exact Test (e)		P<0.001	P<0.001
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/50 (16%)	4/50 (8%)	19/50 (38%)
Adjusted Rates (c)	26.7%	18.5%	68.4%
Terminal Rates (d)	8/30 (27%)	3/20 (15%)	13/21 (62%)
Day of First Observation	731	691	366
Life Table Tests (e)	P<0.001	P=0.413N	P<0.001
Logistic Regression Tests (e)	P=0.002	P=0.375N	P=0.004
Cochran-Armitage Trend Test (e)	P=0.005		
Fisher Exact Test (e)		P=0.178N	P=0.012
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	13/50 (26%)	12/50 (24%)
Adjusted Rates (c)	19.4%	45.9%	38.3%
Terminal Rates (d)	5/30 (17%)	6/20 (30%)	5/21 (24%)
Day of First Observation	729	455	502
Life Table Tests (e)	P=0.027	P=0.012	P=0.031
Logistic Regression Tests (e)	P=0.064	P=0.023	P=0.078
Cochran-Armitage Trend Test (e)	P=0.087		
Fisher Exact Test (e)		P=0.062	P=0.096
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	17/50 (34%)	26/50 (52%)
Adjusted Rates (c)	38.7%	59.3%	76.8%
Terminal Rates (d)	11/30 (37%)	9/20 (45%)	14/21 (67%)
Day of First Observation	729	455	366
Life Table Tests (e)	P<0.001	P=0.023	P<0.001
Logistic Regression Tests (e)	P<0.001	P=0.055	P=0.001
Cochran-Armitage Trend Test (e)	P=0.003		
Fisher Exact Test (e)		P=0.189	P=0.004

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/49 (6%)	6/50 (12%)	11/50 (22%)
Adjusted Rates (c)	10.3%	21.6%	40.1%
Terminal Rates (d)	3/29 (10%)	2/20 (10%)	6/21 (29%)
Day of First Observation	731	600	366
Life Table Tests (e)	P=0.005	P=0.129	P=0.006
Logistic Regression Tests (e)	P=0.010	P=0.184	P=0.015
Cochran-Armitage Trend Test (e)	P=0.015		
Fisher Exact Test (e)		P=0.254	P=0.022
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/49 (4%)	4/50 (8%)	10/50 (20%)
Adjusted Rates (c)	6.3%	18.3%	34.6%
Terminal Rates (d)	1/29 (3%)	3/20 (15%)	4/21 (19%)
Day of First Observation	675	687	589
Life Table Tests (e)	P=0.003	P=0.213	P=0.006
Logistic Regression Tests (e)	P=0.005	P=0.253	P=0.011
Cochran-Armitage Trend Test (e)	P=0.008		
Fisher Exact Test (e)		P=0.349	P=0.015
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	10/50 (20%)	18/50 (36%)
Adjusted Rates (c)	16.3%	37.2%	58.2%
Terminal Rates (d)	4/29 (14%)	5/20 (25%)	9/21 (43%)
Day of First Observation	675	600	366
Life Table Tests (e)	P<0.001	P=0.045	P<0.001
Logistic Regression Tests (e)	P<0.001	P=0.073	P=0.001
Cochran-Armitage Trend Test (e)	P=0.001		
Fisher Exact Test (e)		P=0.140	P=0.002
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (c)	13.3%	0.0%	10.4%
Terminal Rates (d)	4/30 (13%)	0/20 (0%)	1/21 (5%)
Day of First Observation	731		626
Life Table Tests (e)	P=0.539N	P=0.123N	P=0.652N
Logistic Regression Tests (e)	P=0.465N	P=0.123N	P=0.569N
Cochran-Armitage Trend Test (e)	P=0.406N		
Fisher Exact Test (e)		P=0.059N	P=0.500N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	15/50 (30%)	15/50 (30%)	11/50 (22%)
Adjusted Rates (c)	39.4%	46.3%	36.3%
Terminal Rates (d)	8/30 (27%)	4/20 (20%)	5/21 (24%)
Day of First Observation	464	432	485
Life Table Tests (e)	P=0.498N	P=0.271	P=0.520N
Logistic Regression Tests (e)	P=0.247N	P=0.450	P=0.273N
Cochran-Armitage Trend Test (e)	P=0.216N		
Fisher Exact Test (e)		P=0.586N	P=0.247N
Skin: Fibroma or Fibrosarcoma			
Overall Rates (a)	17/50 (34%)	15/50 (30%)	12/50 (24%)
Adjusted Rates (c)	44.9%	46.3%	40.3%
Terminal Rates (d)	10/30 (33%)	4/20 (20%)	6/21 (29%)
Day of First Observation	464	432	485
Life Table Tests (e)	P=0.450N	P=0.384	P=0.480N
Logistic Regression Tests (e)	P=0.193N	P=0.567N	P=0.220N
Cochran-Armitage Trend Test (e)	P=0.161N		
Fisher Exact Test (e)		P=0.415N	P=0.189N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	8/50 (16%)	(b,f) 6/50 (12%)	9/50 (18%)
Adjusted Rates (c)	20.4%		28.8%
Terminal Rates (d)	2/30 (7%)		3/21 (14%)
Day of First Observation	432		257
Life Table Test (e)			P=0.343
Logistic Regression Test (e)			P=0.505
Fisher Exact Test (e)			P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(f) Twenty-six spleens were examined microscopically.

TABLE C4a. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN CONTROL MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls		
Iodinated glycerol (b)	4/50	4/50
Chlorpheniramine maleate (c)	6/50	(d) 7/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	1/50	1/50
Malonaldehyde, sodium salt (c)	3/50	3/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	1/50	(e) 2/50
Methyl carbamate (f)	2/50	2/50
Chlorinated trisodium phosphate (b)	3/50	3/50
TOTAL	20/350 (5.7%)	22/350 (6.3%)
SD (g)	3.55%	3.90%
Range (h)		
High	6/50	7/50
Low	1/50	1/50
Overall Historical Incidence for Untreated Controls		
TOTAL	(i) 73/2,040 (3.6%)	(i,j) 79/2,040 (3.9%)
SD (g)	3.26%	3.22%
Range (h)		
High	6/50	6/50
Low	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Includes one adenocarcinoma, NOS
(e) Includes one papillary adenocarcinoma
(f) Study performed at Microbiological Associates
(g) Standard deviation
(h) Range and SD are presented for groups of 35 or more animals.
(i) Includes five papillary adenomas, five cystadenomas, NOS, and six papillary cystadenomas, NOS
(j) Includes one adenocarcinoma

TABLE C4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	8/50	2/50	10/50
Chlorpheniramine maleate (c)	10/50	6/50	16/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	8/49	10/49	17/49
Malonaldehyde, sodium salt (c)	4/50	14/50	17/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	9/48	10/48	18/48
Methyl carbamate (d)	9/50	5/50	14/50
Chlorinated trisodium phosphate (b)	6/50	9/50	14/50
TOTAL	54/347 (15.6%)	56/347 (16.1%)	106/347 (30.5%)
SD (e)	4.21%	8.03%	5.83%
Range (f)			
High	10/50	14/50	18/48
Low	4/50	2/50	10/50
Overall Historical Incidence for Untreated Controls			
TOTAL	259/2,032 (12.7%)	379/2,032 (18.7%)	609/2,032 (30.0%)
SD (e)	7.21%	6.50%	7.59%
Range (f)			
High	22/50	15/50	29/50
Low	0/49	4/50	8/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN CONTROL MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	8/50	1/50	9/50
Chlorpheniramine maleate (c)	12/50	5/50	16/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	1/50	3/50	4/50
Malonaldehyde, sodium salt (c)	7/47	5/47	10/47
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	5/50	2/50	7/50
Methyl carbamate (d)	11/50	0/50	11/50
Chlorinated trisodium phosphate (b)	2/50	6/50	8/50
TOTAL	46/347 (13.3%)	22/347 (6.3%)	65/347 (18.7%)
SD (e)	8.42%	4.63%	7.51%
Range (f)			
High	12/50	6/50	16/50
Low	1/50	0/50	4/50
Overall Historical Incidence for Untreated Controls			
TOTAL	255/2,034 (12.5%)	102/2,034 (5.0%)	348/2,034 (17.1%)
SD (e)	6.15%	3.42%	7.26%
Range (f)			
High	14/50	8/50	17/50
Low	1/50	0/50	3/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE C4d. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN CONTROL MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/49	0/49	0/49
Chlorpheniramine maleate (c)	1/50	1/50	2/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/47	1/47	1/47
Malonaldehyde, sodium salt (c)	0/44	0/44	0/44
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/41	0/41	0/41
Methyl carbamate (d)	2/50	0/50	2/50
Chlorinated trisodium phosphate (b)	3/50	0/50	3/50
TOTAL	6/331 (1.5%)	2/331 (0.6%)	8/331 (2.4%)
SD (e)	2.43%	1.01%	2.43%
Range (f)			
High	3/50	1/47	3/50
Low	0/50	0/50	0/49
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 7/1,986 (0.4%)	1/1,986 (0.1%)	(g) 8/1,986 (0.4%)
SD (e)	0.91%	0.31%	0.94%
Range (f)			
High	2/49	1/50	2/49
Low	0/50	0/50	3/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one papilloma, NOS

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(44)	(12)	(33)
Inflammation, chronic active	1 (2%)		1 (3%)
Intestine large, colon	(45)	(16)	(43)
Parasite metazoan			1 (2%)
Intestine large, rectum	(43)	(11)	(42)
Parasite metazoan			1 (2%)
Liver	(50)	(50)	(50)
Basophilic focus	1 (2%)		
Clear cell focus			1 (2%)
Cyst		1 (2%)	
Hematopoietic cell proliferation		2 (4%)	1 (2%)
Hemorrhage	1 (2%)		
Hepatodiaphragmatic nodule	2 (4%)		
Inflammation, chronic			1 (2%)
Inflammation, necrotizing		1 (2%)	
Leukocytosis	2 (4%)		3 (6%)
Mineralization	1 (2%)		
Necrosis, coagulative	5 (10%)	3 (6%)	8 (16%)
Pigmentation, hematoidin	1 (2%)		
Vacuolization cytoplasmic			2 (4%)
Mesentery	(43)	(18)	(49)
Inflammation, chronic active	1 (2%)		3 (6%)
Necrosis			1 (2%)
Pancreas	(49)	(21)	(47)
Cyst		1 (5%)	
Inflammation, chronic active			1 (2%)
Necrosis, coagulative		1 (5%)	1 (2%)
Acinus, atrophy	1 (2%)		
Salivary glands	(49)	(20)	(50)
Inflammation, chronic active		1 (5%)	
Necrosis, coagulative			1 (2%)
Stomach, forestomach	(50)	(49)	(48)
Acanthosis	20 (40%)	23 (47%)	26 (54%)
Acanthosis, multiple			1 (2%)
Hyperkeratosis	4 (8%)	1 (2%)	8 (17%)
Inflammation, chronic active	2 (4%)	1 (2%)	
Stomach, glandular	(50)	(20)	(45)
Cyst		1 (5%)	
Inflammation, chronic active			1 (2%)
Tooth	(50)	(20)	(50)
Dysplasia	2 (4%)		8 (16%)
Foreign body			1 (2%)
Inflammation, chronic active	4 (8%)		2 (4%)
CARDIOVASCULAR SYSTEM			
Blood vessel	(47)	(19)	(34)
Mesenteric artery, inflammation, chronic active	1 (2%)		
Mesenteric artery, necrosis, fibrinoid	1 (2%)		
Pulmonary artery, inflammation, chronic active	1 (2%)		
Pulmonary artery, necrosis, fibrinoid	1 (2%)		
Renal artery, inflammation, chronic active	1 (2%)		
Renal artery, necrosis, fibrinoid	1 (2%)		
Renal artery, thrombus	1 (2%)		
Thoracic, inflammation, chronic active	1 (2%)		
Thoracic, necrosis, fibrinoid	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM (Continued)			
Heart	(50)	(20)	(50)
Cardiomyopathy, chronic			4 (8%)
Inflammation, suppurative			2 (4%)
Mineralization	1 (2%)		
Atrium, thrombus	1 (2%)		
Coronary artery, inflammation, chronic active	1 (2%)		
Coronary artery, necrosis, fibrinoid	1 (2%)		
Valve, bacterium	1 (2%)	2 (10%)	4 (8%)
Valve, inflammation, suppurative		2 (10%)	
Valve, thrombus	1 (2%)	2 (10%)	5 (10%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(48)	(21)	(48)
Accessory adrenal cortical nodule	1 (2%)		2 (4%)
Hyperplasia	2 (4%)	1 (5%)	1 (2%)
Hypertrophy	3 (6%)		5 (10%)
Adrenal gland, medulla	(48)	(20)	(50)
Hyperplasia	3 (6%)	1 (5%)	5 (10%)
Islets, pancreatic	(50)	(19)	(47)
Hyperplasia			2 (4%)
Pituitary gland	(48)	(14)	(42)
Pars distalis, cyst	2 (4%)		2 (5%)
Pars distalis, hyperplasia	1 (2%)		
Thyroid gland	(50)	(20)	(49)
Inflammation, chronic active	1 (2%)		
Necrosis, fibrinoid	1 (2%)		
Ultimobranchial cyst		1 (5%)	
Follicular cell, hyperplasia	1 (2%)		5 (10%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	(26)	(18)	(46)
Dilatation			2 (4%)
Inflammation, suppurative			1 (2%)
Epididymis	(50)	(20)	(50)
Inflammation, chronic active		1 (5%)	
Penis	(3)	(2)	(4)
Inflammation, chronic active		1 (50%)	1 (25%)
Mineralization	1 (33%)		
Preputial gland	(3)	(9)	(6)
Inflammation, chronic active	3 (100%)	1 (11%)	4 (67%)
Duct, ectasia		1 (11%)	
Lymphatic, ectasia		1 (11%)	1 (17%)
Prostate	(49)	(20)	(50)
Inflammation, chronic active	4 (8%)	3 (15%)	1 (2%)
Artery, necrosis, fibrinoid	1 (2%)		
Seminal vesicle	(29)	(18)	(36)
Dilatation	5 (17%)	1 (6%)	4 (11%)
Inflammation, chronic active	2 (7%)	1 (6%)	1 (3%)
Inflammation, suppurative	1 (3%)		
Testes	(50)	(20)	(50)
Mineralization		1 (5%)	
Interstitial cell, hyperplasia	1 (2%)	1 (5%)	
Seminiferous tubule, atrophy	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Blood	(3)	(2)	
Neutrophilia	1 (33%)	2 (100%)	
Bone marrow	(50)	(20)	(50)
Femoral, hyperplasia	2 (4%)	3 (15%)	6 (12%)
Lymph node	(49)	(32)	(50)
Hematopoietic cell proliferation		1 (3%)	
Axillary, hemorrhage, acute			1 (2%)
Axillary, hyperplasia, lymphoid			1 (2%)
Lumbar, hyperplasia, plasma cell		1 (3%)	
Mandibular, hematopoietic cell proliferation		1 (3%)	
Mandibular, hyperplasia		1 (3%)	
Mandibular, hyperplasia, lymphoid	1 (2%)		1 (2%)
Mandibular, hyperplasia, plasma cell	1 (2%)		3 (6%)
Mandibular, inflammation, suppurative	1 (2%)		
Mandibular, necrosis	1 (2%)		
Mediastinal, inflammation, suppurative	2 (4%)		
Renal, hematopoietic cell proliferation		1 (3%)	
Lymph node, mesenteric	(19)	(17)	(24)
Angiectasis	10 (53%)	10 (59%)	14 (58%)
Hematopoietic cell proliferation	11 (58%)	11 (65%)	10 (42%)
Hyperplasia, lymphoid	1 (5%)		1 (4%)
Hyperplasia, reticulum cell	1 (5%)		
Spleen	(50)	(26)	(50)
Depletion lymphoid	2 (4%)		
Fibrosis			1 (2%)
Hematopoietic cell proliferation	11 (22%)	13 (50%)	38 (76%)
Infarct			2 (4%)
Necrosis	1 (2%)	1 (4%)	
Thymus	(36)	(13)	(39)
Cyst	3 (8%)		
Necrosis	1 (3%)	6 (46%)	
INTEGUMENTARY SYSTEM			
Skin	(50)	(33)	(50)
Abscess		2 (6%)	
Acanthosis	3 (6%)		1 (2%)
Alopecia	1 (2%)		
Edema			1 (2%)
Fibrosis	1 (2%)		2 (4%)
Hyperkeratosis	2 (4%)		1 (2%)
Inflammation, chronic active	7 (14%)	9 (27%)	6 (12%)
Inflammation, suppurative	1 (2%)	1 (3%)	2 (4%)
Metaplasia, osseous		1 (3%)	
Necrosis, coagulative	1 (2%)		
Lymphatic, ectasia	1 (2%)		
Prepuce, concretion		1 (3%)	
Prepuce, dilatation		1 (3%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(34)	(50)
Joint, femur, tibia, metaplasia, osseous	1 (2%)	1 (3%)	
Joint, tarsal, metaplasia, osseous	24 (48%)	16 (47%)	11 (22%)
Sternum, developmental malformation		1 (3%)	
NERVOUS SYSTEM			
Brain	(50)	(20)	(50)
Hemorrhage, acute	1 (2%)		
Inflammation, chronic active	1 (2%)		
Artery, cerebrum, necrosis, fibrinoid	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM (Continued)			
Peripheral nerve	(47)	(39)	(43)
Sciatic, degeneration		1 (3%)	3 (7%)
Spinal cord	(48)	(20)	(49)
White matter, degeneration	2 (4%)		3 (6%)
RESPIRATORY SYSTEM			
Lung	(49)	(50)	(50)
Hemorrhage, acute	2 (4%)		2 (4%)
Inflammation, chronic	8 (16%)	12 (24%)	20 (40%)
Leukocytosis	1 (2%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	10 (20%)	17 (34%)	19 (38%)
Nose	(50)	(20)	(50)
Foreign body		1 (5%)	
Granuloma		1 (5%)	
Inflammation, chronic active	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation, suppurative	3 (6%)	1 (5%)	3 (6%)
SPECIAL SENSES SYSTEM			
Eye	(1)	(2)	(4)
Cornea, inflammation, chronic active			1 (25%)
Lens, cataract		2 (100%)	1 (25%)
Retina, atrophy		1 (50%)	
Harderian gland	(48)	(49)	(50)
Hyperplasia	1 (2%)		2 (4%)
URINARY SYSTEM			
Kidney	(50)	(22)	(50)
Atrophy			1 (2%)
Bacterium		1 (5%)	
Cyst			1 (2%)
Hemorrhage	1 (2%)		
Hydronephrosis	1 (2%)	1 (5%)	
Infarct	2 (4%)	3 (14%)	8 (16%)
Inflammation, suppurative	3 (6%)	3 (14%)	1 (2%)
Mineralization		3 (14%)	8 (16%)
Nephropathy, chronic	21 (42%)	4 (18%)	22 (44%)
Thrombus			1 (2%)
Artery, inflammation, chronic active	2 (4%)		
Artery, necrosis, fibrinoid	2 (4%)		
Ureter	(39)	(15)	(38)
Inflammation, chronic active	1 (3%)		
Inflammation, suppurative	1 (3%)		
Urethra	(30)	(8)	(35)
Concretion	2 (7%)	4 (50%)	
Inflammation, chronic active	1 (3%)	2 (25%)	1 (3%)
Inflammation, suppurative			1 (3%)
Urinary bladder	(49)	(21)	(49)
Dilatation	3 (6%)	8 (38%)	2 (4%)
Inflammation, chronic active	2 (4%)	1 (5%)	

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	49
ALIMENTARY SYSTEM			
Gallbladder	(45)	*(50)	(39)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Intestine large, cecum	(46)	*(50)	(42)
Leiomyoma		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		
Intestine large, rectum	(46)	*(50)	(43)
Lymphoma malignant mixed			1 (2%)
Intestine small, duodenum	(44)	*(50)	(41)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
Intestine small, ileum	(44)	*(50)	(43)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Intestine small, jejunum	(45)	*(50)	(42)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Liver	(50)	(50)	(49)
Adenocarcinoma, metastatic, mammary gland	1 (2%)		
Hemangioma, multiple	1 (2%)		
Hemangiosarcoma	1 (2%)	1 (2%)	
Hemangiosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma	3 (6%)	3 (6%)	2 (4%)
Hepatocellular adenoma	2 (4%)	3 (6%)	15 (31%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant histiocytic	3 (6%)	2 (4%)	6 (12%)
Lymphoma malignant lymphocytic	2 (4%)	4 (8%)	3 (6%)
Lymphoma malignant mixed	1 (2%)	1 (2%)	1 (2%)
Mesentery	*(50)	*(50)	*(49)
Fibrosarcoma, metastatic, skin			1 (2%)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)		2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		2 (4%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	2 (4%)		4 (8%)
Pancreas	(50)	*(50)	(47)
Fibrosarcoma, metastatic, skin			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	3 (6%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	1 (2%)		3 (6%)
Salivary glands	(50)	*(50)	(47)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic	4 (8%)	1 (2%)	2 (4%)
Lymphoma malignant mixed	2 (4%)		1 (2%)
Stomach, forestomach	(46)	*(50)	(44)
Papilloma squamous			2 (5%)
Tongue	*(50)	*(50)	*(49)
Papilloma squamous			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant mixed			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	*(50)	(48)
Pheochromocytoma benign		1 (2%)	
Adrenal gland, cortex	(50)	*(50)	(47)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)		
Capsule, carcinoma			1 (2%)
Islets, pancreatic	(50)	*(50)	(47)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	2 (4%)		1 (2%)
Pituitary gland	(49)	*(50)	(43)
Pars distalis, adenoma	12 (24%)	5 (10%)	4 (9%)
Pars distalis, adenoma, multiple	1 (2%)		
Pars intermedia, adenoma			1 (2%)
Pars intermedia, carcinoma	1 (2%)		1 (2%)
Thyroid gland	(48)	*(50)	(48)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant mixed			1 (2%)
Bilateral, follicular cell, adenoma, multiple	1 (2%)		
Follicular cell, adenoma	3 (6%)		3 (6%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	*(50)	*(50)	*(49)
Adenocarcinoma		1 (2%)	
Ovary	(50)	(45)	(47)
Granulosa cell tumor benign		5 (11%)	5 (11%)
Lymphoma malignant histiocytic	1 (2%)		3 (6%)
Lymphoma malignant lymphocytic	1 (2%)	2 (4%)	4 (9%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed			1 (2%)
Uterus	(50)	*(50)	(49)
Hemangioma		1 (2%)	
Hemangiosarcoma	1 (2%)	1 (2%)	
Leiomyoma		1 (2%)	
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed			2 (4%)
Polyp stromal	2 (4%)	1 (2%)	
Vagina	*(50)	*(50)	*(49)
Lymphoma malignant histiocytic		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(48)
Femoral, hemangiosarcoma			1 (2%)
Femoral, lymphoma malignant histiocytic			1 (2%)
Femoral, lymphoma malignant lymphocytic			1 (2%)
Vertebral, hemangiosarcoma			1 (2%)
Vertebral, lymphoma malignant histiocytic			2 (4%)
Vertebral, lymphoma malignant lymphocytic			1 (2%)
Vertebral, lymphoma malignant mixed			1 (2%)
Lymph node	(50)	*(50)	(46)
Deep cervical, lymphoma malignant histiocytic	1 (2%)		
Deep cervical, lymphoma malignant lymphocytic		1 (2%)	1 (2%)
Iliac, lymphoma malignant mixed			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	*(50)	(46)
Inguinal, lymphoma malignant histiocytic			1 (2%)
Inguinal, lymphoma malignant lymphocytic		2 (4%)	1 (2%)
Inguinal, lymphoma malignant mixed	1 (2%)		
Lumbar, lymphoma malignant lymphocytic	1 (2%)	2 (4%)	1 (2%)
Lumbar, lymphoma malignant		1 (2%)	
Lumbar, lymphoma malignant mixed	1 (2%)		
Mandibular, lymphoma malignant histiocytic	2 (4%)		3 (7%)
Mandibular, lymphoma malignant lymphocytic	5 (10%)	2 (4%)	7 (15%)
Mandibular, lymphoma malignant		1 (2%)	
Mandibular, lymphoma malignant mixed	3 (6%)		7 (15%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Mediastinal, hepatocellular carcinoma, metastatic, liver	1 (2%)		
Mediastinal, lymphoma malignant histiocytic	2 (4%)	1 (2%)	2 (4%)
Mediastinal, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	2 (4%)
Mediastinal, lymphoma malignant		1 (2%)	
Mediastinal, lymphoma malignant mixed	2 (4%)		6 (13%)
Pancreatic, lymphoma malignant histiocytic			2 (4%)
Pancreatic, lymphoma malignant lymphocytic		1 (2%)	
Pancreatic, lymphoma malignant		1 (2%)	
Pancreatic, lymphoma malignant mixed			1 (2%)
Renal, lymphoma malignant histiocytic	1 (2%)	1 (2%)	2 (4%)
Renal, lymphoma malignant lymphocytic	1 (2%)	2 (4%)	1 (2%)
Renal, lymphoma malignant		1 (2%)	
Renal, lymphoma malignant mixed	1 (2%)		2 (4%)
Lymph node, mesenteric	(11)	*(50)	(13)
Lymphoma malignant histiocytic	5 (45%)	1 (2%)	3 (23%)
Lymphoma malignant lymphocytic	1 (9%)	2 (4%)	3 (23%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	2 (18%)		6 (46%)
Spleen	(50)	*(50)	(48)
Hemangiosarcoma			1 (2%)
Hemangiosarcoma, metastatic, skin		1 (2%)	
Lymphoma malignant histiocytic	5 (10%)	1 (2%)	5 (10%)
Lymphoma malignant lymphocytic	7 (14%)	6 (12%)	6 (13%)
Lymphoma malignant mixed	3 (6%)		8 (17%)
Thymus	(48)	*(50)	(38)
Lymphoma malignant histiocytic	3 (6%)	1 (2%)	2 (5%)
Lymphoma malignant lymphocytic	5 (10%)		3 (8%)
Lymphoma malignant mixed	3 (6%)		2 (5%)
INTEGUMENTARY SYSTEM			
Mammary gland	(29)	(48)	(33)
Adenoacanthoma		1 (2%)	1 (3%)
Adenocarcinoma	1 (3%)		1 (3%)
Adenoma	2 (7%)	4 (8%)	
Fibroadenoma	1 (3%)		
Skin	(50)	*(50)	(48)
Lymphoma malignant		1 (2%)	
Sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, fibrosarcoma	2 (4%)	2 (4%)	4 (8%)
Subcutaneous tissue, fibrosarcoma, multiple			1 (2%)
Subcutaneous tissue, hemangiosarcoma		3 (6%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(49)
Fibrosarcoma, metastatic, skin	1 (2%)	1 (2%)	2 (4%)
Hemangiosarcoma			1 (2%)
Lymphoma malignant histiocytic	2 (4%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	*(50)	(48)
Carcinoma, metastatic, pituitary gland			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Meningioma benign			1 (2%)
Peripheral nerve	(47)	(43)	(42)
Sciatic, lymphoma malignant mixed			1 (2%)
Spinal cord	(50)	*(50)	(49)
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(49)
Adenoacanthoma, metastatic, mammary gland		1 (2%)	
Adenocarcinoma, metastatic, mammary gland	1 (2%)		
Alveolar/bronchiolar adenoma	4 (8%)	3 (6%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	4 (8%)	7 (14%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	
Basosquamous tumor malignant		1 (2%)	
Carcinoma, metastatic, harderian gland		1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)
Hemangiosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant histiocytic	3 (6%)	1 (2%)	4 (8%)
Lymphoma malignant lymphocytic	5 (10%)	2 (4%)	2 (4%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	1 (2%)		1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Mediastinum, hemangiosarcoma	1 (2%)		
Mediastinum, lymphoma malignant histiocytic			1 (2%)
Mediastinum, lymphoma malignant lymphocytic			1 (2%)
Mediastinum, lymphoma malignant mixed			1 (2%)
Nose	(50)	*(50)	(48)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	(47)	(45)	(48)
Adenoma	5 (11%)	6 (13%)	12 (25%)
Adenoma, multiple		1 (2%)	1 (2%)
Carcinoma		3 (7%)	2 (4%)
Bilateral, adenoma		1 (2%)	7 (15%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	*(50)	(48)
Lymphoma malignant histiocytic	2 (4%)		4 (8%)
Lymphoma malignant lymphocytic	4 (8%)	3 (6%)	5 (10%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	3 (6%)		5 (10%)
Urinary bladder	(43)	*(50)	(47)
Lymphoma malignant histiocytic	1 (2%)		2 (4%)
Lymphoma malignant lymphocytic	2 (5%)		1 (2%)
Lymphoma malignant		1 (2%)	
Lymphoma malignant mixed	1 (2%)		1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(49)
Lymphoma malignant histiocytic	5 (10%)	2 (4%)	6 (12%)
Lymphoma malignant mixed	4 (8%)	1 (2%)	9 (18%)
Lymphoma malignant lymphocytic	7 (14%)	7 (14%)	8 (16%)
Lymphoma malignant undifferentiated cell	1 (2%)		
Hemangiosarcoma	4 (8%)	5 (10%)	1 (2%)
Hemangioma	1 (2%)	1 (2%)	
Lymphoma malignant		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	41	35	33
Dead	5	9	10
Moribund	3	6	6
Accident	1		
Missing			1
TUMOR SUMMARY			
Total animals with primary neoplasms **	33	41	47
Total primary neoplasms	66	67	105
Total animals with benign neoplasms	24	24	39
Total benign neoplasms	36	35	61
Total animals with malignant neoplasms	24	26	33
Total malignant neoplasms	30	32	44
Total animals with secondary neoplasms ***	2	7	5
Total secondary neoplasms	5	9	9

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: VEHICLE CONTROL

WEEKS ON STUDY	058	081	094	097	098	099	099	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	205	161	112	141	182	121	125	132	181	111	114	124	131	133	152	155	164	171	172	174	183	191	193	195	202
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Lymphoma malignant lymphocytic									X																
Intestine large, colon	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Intestine large, rectum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Intestine small	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Intestine small, ileum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Lymphoma malignant undifferentiated cell type								X																	
Intestine small, jejunum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Lymphoma malignant histiocytic			X																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland								X																	
Hemangioma, multiple																									
Hemangiosarcoma																									
Hepatocellular carcinoma				X				X																	
Hepatocellular adenoma																							X		
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic			X		X																				
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
Mesentery		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X															X	
Lymphoma malignant mixed											X														
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Stomach, glanduiar	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+			+		+			+		+		+	+	+	+	+				+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant mixed									X																
Parathyroid gland	+	+	+	M	+	M	M	M	M	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X											X					X	X
Pars distalis, adenoma, multiple						X																			
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Bilateral, follicular cell, adenoma, multiple																									
Follicular cell, adenoma			X																						
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X																
Oviduct	+		+	+	+		+			+	+		+	+	+	+	+	+		+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Polyp stromal																		X							
Vagina																									

+: Tissue examined microscopically
: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	204	134	143	144	151	153	154	162	163	173	175	184	185	192	194	201	113	115	122	123	135	142	145	165	203	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																			X							1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic																										1
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+	44
Lymphoma malignant undifferentiated cell type																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+	45
Lymphoma malignant histiocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																										1
Hemangioma, multiple	X																									1
Hemangiosarcoma																					X					1
Hepatocellular carcinoma															X											3
Hepatocellular adenoma																				X						2
Hepatocellular adenoma, multiple																									X	1
Lymphoma malignant histiocytic																	X									3
Lymphoma malignant lymphocytic																		X								2
Lymphoma malignant mixed																			X							1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																			X							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																	X									2
Lymphoma malignant lymphocytic	X													X												4
Lymphoma malignant mixed																			X							2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		+	+	+	+	+	+	+	+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	47
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+		+		+				+	+			+					+	+	+		+		+	27
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																			X							1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																			X							2
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	M	M	+	M	+	M	M	+	+	M	M	M	+	+	M	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X								X	X	X			X	X					X				X	12
Pars distalis, adenoma, multiple																										1
Pars intermedia, carcinoma														X												1
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																	X									1
Bilateral, follicular cell, adenoma, multiple																					X					1
Follicular cell, adenoma															X					X						3
GENERAL BODY SYSTEM																										
Tissue, NOS									+																	1
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Oviduct	+	+	+		+	+	+	+	+		+	+			+	+	+	+	+	+	+	+	+	+	+	40
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Polyp stromal																							X			2
Vagina			+																							1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	058	081	094	097	098	099	099	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	205	161	112	141	182	121	125	132	181	111	114	124	131	133	152	155	164	171	172	174	183	191	193	195	202
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, lymphoma malignant histiocytic					X																				
Inguinal, lymphoma malignant mixed																									
Lumbar, lymphoma malignant lymphocytic									X																
Lumbar, lymphoma malignant mixed																									
Mandibular, lymphoma malignant histiocytic					X																				
Mandibular, lymphoma malignant lymphocytic									X													X			
Mandibular, lymphoma malignant mixed											X														
Mediastinal, hepatocellular carcinoma, metastatic, liver								X																	
Mediastinal, lymphoma malignant histiocytic					X																				
Mediastinal, lymphoma malignant lymphocytic									X																
Mediastinal, lymphoma malignant mixed											X														
Renal, lymphoma malignant histiocytic					X																				
Renal, lymphoma malignant lymphocytic									X																
Renal, lymphoma malignant mixed																									
Lymph node, mesenteric	M	M	+	M	+	+	M	A	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Lymphoma malignant histiocytic			X		X																				
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X		X																				
Lymphoma malignant lymphocytic									X								X					X		X	
Lymphoma malignant mixed											X														
Thymus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic									X													X		X	
Lymphoma malignant mixed											X														
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	M	M	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	+	M	+	M
Adenocarcinoma								X																	
Adenoma													X												
Fibroadenoma								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibrosarcoma						X									X										
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin						X																			
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland								X																	
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver								X																	
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X								X							X	
Lymphoma malignant mixed																									
Mediastinum, hemangiosarcoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							X
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed											X														
Ureter				+											+				+		+		+		+
Urinary bladder	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed											X														

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	204	134	143	144	151	153	154	162	163	173	175	184	185	192	194	201	113	115	122	123	135	142	145	165	203
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deep cervical, lymphoma malignant histiocytic																									1
Inguinal, lymphoma malignant mixed									X																1
Lumbar, lymphoma malig. lymphocytic																									1
Lumbar, lymphoma malignant mixed									X																1
Mandibular, lymphoma malignant histiocytic																							X		2
Mandibular, lymphoma malignant lymphocytic	X													X				X							5
Mandibular, lymphoma malig. mixed									X										X						3
Mediastinal, hepatocellular carcinoma, metastatic, liver																									1
Mediastinal, lymphoma malignant histiocytic																	X								2
Mediastinal, lymphoma malignant lymphocytic																									1
Mediastinal, lymphoma malig. mixed																			X						2
Renal, lymphoma malignant histiocytic																									1
Renal, lymphoma malig. lymphocytic																									1
Renal, lymphoma malignant mixed									X																1
Lymph node, mesenteric	M	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	+	M	+	M	M	M	+	M	+	11
Lymphoma malignant histiocytic																	X						X		X	5
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed									X										X							2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																	X						X		X	5
Lymphoma malignant lymphocytic	X													X				X								7
Lymphoma malignant mixed									X										X							3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																	X						X		X	3
Lymphoma malignant lymphocytic	X													X												5
Lymphoma malignant mixed									X										X							3
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	M	+	M	M	M	M	+	M	+	+	+	+	M	M	M	+	+	M	+	M	+	+	+	29
Adenocarcinoma																										1
Adenoma																							X			2
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma															X											1
Subcutaneous tissue, fibrosarcoma																										2
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																	X									2
Lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																										1
Alveolar/bronchiolar adenoma	X											X					X									4
Alveolar/bronchiolar carcinoma										X					X											2
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																	X								X	3
Lymphoma malignant lymphocytic	X													X												5
Lymphoma malignant mixed																			X							1
Mediastinum, hemangiosarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma									X										X		X					5
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																	X									2
Lymphoma malignant lymphocytic	X													X				X								4
Lymphoma malignant mixed									X										X							3
Ureter						+							+	M	+								+			10
Urinary bladder	+	+	M		+		+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		+	+	+	43
Lymphoma malignant histiocytic																	X									1
Lymphoma malignant lymphocytic														X												2
Lymphoma malignant mixed																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: LOW DOSE

WEEKS ON STUDY	050	061	079	085	085	088	096	097	098	099	099	100	101	102	103	105	105	105	105	105	105	105	105	105
CARCASS ID	395	345	381	361	383	331	325	391	313	321	354	404	323	382	372	314	322	333	341	343	352	373	374	384	393
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+																			
Gallbladder	+	+	A	+	+	A																			
Intestine large	+	+	+	+	+	+																			
Intestine large, cecum	+	+	A	+	+	M																			
Leiomyoma																									
Intestine large, colon	+	+	+	+	+	+																			
Intestine large, rectum	+	+	+	+	+	+																			
Intestine small	+	+	+	+	+	+																			
Intestine small, duodenum	+	+	A	+	+	+																			
Lymphoma malignant lymphocytic				X																					
Intestine small, ileum	+	+	A	+	+	M																			
Intestine small, jejunum	+	+	A	+	+	M																			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Hemangiosarcoma, metastatic, skin										X															
Hepatocellular carcinoma																X			X						
Hepatocellular adenoma						X									X										
Hepatocellular adenoma, multiple																	X								
Lymphoma malignant histiocytic								X				X													
Lymphoma malignant lymphocytic				X			X							X											
Lymphoma malignant mixed																							X		
Mesentery	+	+	+	+	+	+																			
Lymphoma malignant						X																			
Pancreas	+	+	+	+	+	+																			
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant						X																			
Salivary glands	+	+	+	+	+	+	+																		
Lymphoma malignant lymphocytic							X																		
Stomach	+	+	+	+	+	+																			
Stomach, forestomach	+	+	+	+	+	+																			
Stomach, glandular	+	+	+	+	+	A																			
Tooth	+	+	+	+	+	+																			
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+																			
Heart	+	+	+	+	+	+																			
Alveolar/bronchiolar carcinoma, metastatic, lung		X																							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+									+										
Pheochromocytoma benign															X										
Adrenal gland, cortex	+	+	+	+	+	+																			
Adrenal gland, medulla	+	+	+	+	+	+																			
Islets, pancreatic	+	+	+	+	+	+																			
Lymphoma malignant						X																			
Parathyroid gland	+	+	+	+	+	M																			
Pituitary gland	+	+	+	+	+	+				+	+					+						+			+
Pars distalis, adenoma											X											X			X
Thyroid gland	+	+	+	+	+	+																			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland																									
Adenocarcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Granulosa cell tumor benign																				X		X			
Lymphoma malignant lymphocytic							X							X											
Lymphoma malignant						X																			
Oviduct	+	+	+	+	+	+																			
Uterus	+	+	+	+	+	+	+		+	+			+		+		+	+	+	+		+	+		+
Hemangioma																									
Hemangiosarcoma			X																						
Leiomyoma																									
Polyp stromal																									
Vagina			+					+																	
Lymphoma malignant histiocytic								X																	

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	394	401	405	311	315	332	335	342	353	362	365	392	403	312	324	334	344	351	355	363	364	371	375	385	402	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										6
Gallbladder																										4
Intestine large																	+									7
Intestine large, cecum																	+									5
Leiomyoma																	X									1
Intestine large, colon																										6
Intestine large, rectum																										6
Intestine small																										6
Intestine small, duodenum																										5
Lymphoma malignant lymphocytic																										1
Intestine small, ileum																										4
Intestine small, jejunum																										4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, skin																										1
Hepatocellular carcinoma													X													3
Hepatocellular adenoma							X																			3
Hepatocellular adenoma, multiple																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic								X																		4
Lymphoma malignant mixed																										1
Mesentery																										6
Lymphoma malignant																										1
Pancreas																										6
Lymphoma malignant lymphocytic																										1
Lymphoma malignant																										1
Salivary glands																										7
Lymphoma malignant lymphocytic																										1
Stomach																										6
Stomach, forestomach																										6
Stomach, glandular																										5
Tooth																										6
CARDIOVASCULAR SYSTEM																										
Blood vessel																										6
Heart																										6
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
ENDOCRINE SYSTEM																										
Adrenal gland																										7
Pheochromocytoma benign																										1
Adrenal gland, cortex																										6
Adrenal gland, medulla																										6
Islets, pancreatic																										6
Lymphoma malignant																										1
Parathyroid gland																										5
Pituitary gland						+													+				+			14
Pars distalis, adenoma						X																	X			5
Thyroid gland																										6
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																+										1
Adenocarcinoma																X										1
Ovary	+	+	+	+	+	I	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	45
Granulosa cell tumor benign							X			X															X	5
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Oviduct																										6
Uterus		+		+			+		+	+	+	+	+	+	+	+	+		+	+	+		+		+	35
Hemangioma																							X			1
Hemangiosarcoma																										1
Leiomyoma																					X					1
Polyp stromal															X											1
Vagina																										2
Lymphoma malignant histiocytic																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	050	061	079	085	085	088	096	097	098	099	099	100	101	102	103	105	105	105	105	105	105	105	105	105	105
CARCASS ID	395	345	381	361	383	331	325	391	313	321	354	404	323	382	372	314	322	333	341	343	352	373	374	384	393
HEMATOPOIETIC SYSTEM																									
Blood				+	+																				
Bone marrow	+	+	+	+	+	+																			
Lymph node	+	+	+	+	+	+	+	+				+		+											
Deep cervical, lymphoma malignant lymphocytic							X																		
Inguinal, lymphoma malignant lymphocytic							X																		
Lumbar, lymphoma malignant lymphocytic							X							X											
Lumbar, lymphoma malignant						X																			
Mandibular, lymphoma malignant lymphocytic							X							X											
Mandibular, lymphoma malignant						X																			
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		X																							
Mediastinal, lymphoma malignant histiocytic												X													
Mediastinal, lymphoma malignant lymphocytic							X																		
Mediastinal, lymphoma malignant						X																			
Pancreatic, lymphoma malignant lymphocytic				X																					
Pancreatic, lymphoma malignant						X																			
Renal, lymphoma malignant histiocytic												X													
Renal, lymphoma malignant lymphocytic							X							X											
Renal, lymphoma malignant						X																			
Lymph node, mesenteric	M	M	M	+	M	+	+	+				+		+											
Lymphoma malignant histiocytic												X													
Lymphoma malignant lymphocytic							X							X											
Lymphoma malignant						X																			
Spleen	+	+	+	+	+	A	+	+		+		+	+	+		+					+	+			
Hemangiosarcoma, metastatic, skin													X												
Lymphoma malignant histiocytic												X													
Lymphoma malignant lymphocytic							X							X							X				
Thymus	+	M	M	M	+	M						+													
Lymphoma malignant histiocytic												X													
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma					X																				
Adenoma						X			X		X			X											
Skin	+	+	+	+	+	+	+		+	+	+		+	+											
Lymphoma malignant						X																			
Subcutaneous tissue, fibrosarcoma	X																								
Subcutaneous tissue, hemangiosarcoma										X			X												
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+																			
Skeletal muscle	+	+	+	+	+	+																			
Fibrosarcoma, metastatic, skin	X																								
Lymphoma malignant						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+			+																
Peripheral nerve	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	I	+	+	+	+	+	+	+	M
Spinal cord	+	+	+	+	+	+																			
RESPIRATORY SYSTEM																									
Larynx						+																			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma, metastatic, mammary gland					X																				
Alveolar/bronchiolar adenoma														X	X										
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma																X	X								
Alveolar/bronchiolar carcinoma, multiple		X																							
Basosquamous tumor malignant					X																				
Carcinoma, metastatic, harderian gland														X											
Hemangiosarcoma, metastatic, skin										X															
Hepatocellular carcinoma, metastatic, liver																X									
Lymphoma malignant histiocytic												X													
Lymphoma malignant lymphocytic							X							X											
Lymphoma malignant						X																			
Nose	+	+	+	+	+	+																			
Trachea	+	+	+	+	+	+																			
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																			X						
Carcinoma														X										X	
Bilateral, adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+							+	+										
Lymphoma malignant lymphocytic							X							X											
Lymphoma malignant						X																			
Urinary bladder	+	+	M	+	+	+		+																	
Lymphoma malignant						X																			

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	394	401	405	311	315	332	335	342	353	362	365	392	403	312	324	334	344	351	355	363	364	371	375	385	402	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Bone marrow																										6
Lymph node					+													+					+			13
Deep cervical, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant lymphocytic																		X								2
Lumbar, lymphoma malig. lymphocytic																										2
Lumbar, lymphoma malignant																										1
Mandibular, lymphoma malignant lymphocytic																										2
Mandibular, lymphoma malignant																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malignant																										1
Pancreatic, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant																										1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malig. lymphocytic																										2
Renal, lymphoma malignant																										1
Lymph node, mesenteric					+																					7
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Spleen			+		+			+	+									+								19
Hemangiosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic			X					X										X								6
Thymus																							+			4
Lymphoma malignant histiocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoacanthoma																										1
Adenoma																										4
Skin					+								+													14
Lymphoma malignant																										1
Subcutaneous tissue, fibrosarcoma													X													2
Subcutaneous tissue, hemangiosarcoma					X																					3
MUSCULOSKELETAL SYSTEM																										
Bone																										6
Skeletal muscle																										6
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant																										1
NERVOUS SYSTEM																										
Brain																										7
Peripheral nerve	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	43
Spinal cord																										6
RESPIRATORY SYSTEM																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma, metastatic, mammary gland																										1
Alveolar/bronchiolar adenoma															X											3
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma						X							X													4
Alveolar/bronchiolar carcinoma, multiple																										1
Basosquamous tumor malignant																										1
Carcinoma, metastatic, harderian gland																										1
Hemangiosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Nose																										6
Trachea																										6
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	45
Adenoma					X		X		X			X	X				X									6
Adenoma, multiple																										1
Carcinoma						X																				3
Bilateral, adenoma								X																		1
URINARY SYSTEM																										
Kidney					+													+								11
Lymphoma malignant lymphocytic																		X								3
Lymphoma malignant																										1
Urinary bladder																										6
Lymphoma malignant																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE: HIGH DOSE

WEEKS ON STUDY	076	076	079	083	085	093	094	094	094	096	096	096	097	102	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	563	593	514	571	535	541	522	603	523	513	572	555	601	591	574	553	595	525	542	552	554	564	583	592	605
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	A	+	+		+	+	A	A	A	+	+	+	+	A	M	+	+	+	+	+	+	+
Intestine large	+	+	A	A	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	+		+	+		A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	A	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	A	+	+		+	+		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Intestine small	+	+	A	A	+	+		+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	A	+	+		+	+		A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic	X																								
Intestine small, ileum	+	+	A	A	+	+		+	+		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	+		+	+		A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic														X											
Lymphoma malignant lymphocytic									X																
Liver	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																					X				
Hepatocellular adenoma								X							X				X	X		X		X	
Hepatocellular adenoma, multiple																					X				
Lymphoma malignant histiocytic						X					X			X	X	X	X								
Lymphoma malignant lymphocytic	X				X				X																
Lymphoma malignant mixed																									
Mesentery	+	+		+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin													X												
Lymphoma malignant histiocytic											X			X											
Lymphoma malignant lymphocytic	X								X																
Lymphoma malignant mixed															X								X		
Pancreas	+	+	A	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin													X												
Lymphoma malignant histiocytic																	X								
Lymphoma malignant lymphocytic	X				X				X																
Lymphoma malignant mixed															X								X		
Salivary glands	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic	X																								
Lymphoma malignant mixed															X										
Stomach	+	+	A	A	+	+		+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	A	+	+		+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																X									
Stomach, glandular	+	+	A	A	+	+		+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue						+																			
Papilloma squamous						X																			
Tooth	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel		+	+	+	+	+		+	+	+	+			+	+	+	+				+	+	+		+
Heart	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Lymphoma malignant histiocytic																X									
Lymphoma malignant mixed															X										
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic														X											
Lymphoma malignant lymphocytic									X																
Capsule, carcinoma																									
Adrenal gland, medulla	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic	X																								
Lymphoma malignant mixed															X										
Parathyroid gland	+	+	M	+	+	M		+	+	+	+	M	M	+	+	+	+	M	M	+	M	M	M	M	+
Pituitary gland	+	M	+	+	+	M		+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Pars intermedia, carcinoma					X																				
Thyroid gland	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant mixed															X										
Follicular cell, adenoma																					X				X
GENERAL BODY SYSTEM																									
Tissue, NOS				+																					
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																					X				
Lymphoma malignant histiocytic											X			X			X								
Lymphoma malignant lymphocytic	X				X				X			X													
Lymphoma malignant mixed															X										
Oviduct			+		+	+		+		A		+		+		+	+	+	+	+		+	+		+
Uterus	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X					X														
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed															X								X		

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	511	521	524	531	532	543	573	581	584	594	602	512	515	533	534	544	545	551	561	562	565	575	582	585	604	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant mixed																									X	1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymphoma malignant lymphocytic																										1
Intestine small, ileum	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																							X			2
Hepatocellular adenoma		X	X	X			X	X		X			X									X			X	15
Hepatocellular adenoma, multiple																							X			2
Lymphoma malignant histiocytic																										6
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed			X																							1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed					X							X														4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed																									X	3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic													X													2
Lymphoma malignant mixed																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Papilloma squamous																X										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Tongue																										1
Papilloma squamous																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARDIOVASCULAR SYSTEM																										
Blood vessel	+		+	+	+	+	+		+		+	+	+				+	+	+	+	+		+	+		34
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Capsule, carcinoma																X										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																								X		2
Lymphoma malignant mixed																										1
Parathyroid gland	M	M	+	M	+	+	M	+	M	M	+	M	+	+	+	+	M	M	+	M	M	+	+	+	+	28
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pars distalis, adenoma												X		X			X			X						4
Pars intermedia, adenoma					X																					1
Pars intermedia, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Follicular cell, adenoma														X												3
GENERAL BODY SYSTEM																										
Tissue, NOS												+						+								3
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Granulosa cell tumor benign															X	X					X			X		5
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic																										4
Lymphoma malignant mixed																										1
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	37
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	076	076	079	083	085	093	094	094	094	096	096	096	097	102	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	563	593	514	571	535	541	522	603	523	513	572	555	601	591	574	553	595	525	542	552	554	564	583	592	605
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																		X							
Femoral, lymphoma malignant histiocytic																X									
Femoral, lymphoma malignant lymphocytic																									
Vertebral, hemangiosarcoma																		X							
Vertebral, lymphoma malignant histiocytic											X						X								
Vertebral, lymphoma malignant lymphocytic																									
Vertebral, lymphoma malignant mixed																							X		
Lymph node	+	+	M	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, lymphoma malignant lymphocytic									X																
Iliac, lymphoma malignant mixed																									
Inguinal, lymphoma malignant histiocytic																	X								
Inguinal, lymphoma malignant lymphocytic	X																								
Lumbar, lymphoma malignant lymphocytic	X																								
Mandibular, lymphoma malignant histiocytic											X					X	X								
Mandibular, lymphoma malignant lymphocytic	X				X				X			X										X			
Mandibular, lymphoma malignant mixed															X								X		
Mediastinal, lymphoma malignant histiocytic											X			X											
Mediastinal, lymphoma malignant lymphocytic									X																
Mediastinal, lymphoma malignant mixed																		X					X		
Pancreatic, lymphoma malignant histiocytic														X			X								
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant histiocytic														X			X								
Renal, lymphoma malignant lymphocytic	X																								
Renal, lymphoma malignant mixed															X										
Lymph node, mesenteric	+	M	M	M	M	M		M	+	M	M	+	M	+	+	+	+	M	+	M	M	M	M	M	M
Lymphoma malignant histiocytic														X		X	X								
Lymphoma malignant lymphocytic	X								X			X													
Lymphoma malignant mixed															X										
Spleen	+	+	+	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Lymphoma malignant histiocytic						X					X			X		X	X								
Lymphoma malignant lymphocytic	X				X				X			X													
Lymphoma malignant mixed															X								X		
Thymus	+	M	+	+	+	M		+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+
Lymphoma malignant histiocytic											X						X								
Lymphoma malignant lymphocytic	X								X																
Lymphoma malignant mixed															X										
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+		M	M	+	M	+	+	M	M	+	M	M	+	M	+	M	M	M	+
Adenoacanthoma										X															
Adenocarcinoma													X												
Skin	+	+	+	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma												X													X
Subcutaneous tissue, fibrosarcoma, multiple													X												
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin													X												X
Hemangiosarcoma																		X							
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed															X										
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland					X																				
Lymphoma malignant histiocytic																X									
Lymphoma malignant lymphocytic	X																								
Meningioma benign		X																							
Peripheral nerve	M	+	M	M	+	+		+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Sciatic, lymphoma malignant mixed															X										
Spinal cord	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X					X														
Lymphoma malignant lymphocytic	X																								
Lymphoma malignant mixed															X										

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	5111	5121	5244	5311	5332	5443	5773	5881	5844	5994	6002	5112	5115	5333	5344	5445	5451	5561	5662	5665	5755	5822	5855	6004		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Femoral, hemangiosarcoma																										1
Femoral, lymphoma malignant histiocytic																										1
Femoral, lymphoma malignant lymphocytic																							X			1
Vertebral, hemangiosarcoma																										1
Vertebral, lymphoma malignant histiocytic																										2
Vertebral, lymphoma malignant lymphocytic																							X			1
Vertebral, lymphoma malignant mixed																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		46
Deep cervical, lymphoma malignant lymphocytic																										1
Iliac, lymphoma malignant mixed					X																					1
Inguinal, lymphoma malignant histiocytic																										1
Inguinal, lymphoma malignant lymphocytic																										1
Lumbar, lymphoma malig. lymphocytic																										1
Mandibular, lymphoma malignant histiocytic																										3
Mandibular, lymphoma malignant lymphocytic												X					X									7
Mandibular, lymphoma malig. mixed			X		X																	X	X	X		7
Mediastinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malignant lymphocytic												X														2
Mediastinal, lymphoma malig. mixed					X						X											X		X		6
Pancreatic, lymphoma malignant histiocytic																										2
Pancreatic, lymphoma malignant mixed											X															1
Renal, lymphoma malignant histiocytic																										2
Renal, lymphoma malig lymphocytic																										1
Renal, lymphoma malignant mixed					X																					2
Lymph node, mesenteric	M	M	+	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	+	+	13
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed			X		X						X												X	X		6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										5
Lymphoma malignant lymphocytic												X					X									6
Lymphoma malignant mixed			X		X						X											X	X	X		8
Thymus	M	M	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	38
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																	X									3
Lymphoma malignant mixed			X																							2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	33
Adenoacanthoma																										1
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibrosarcoma				X							X															4
Subcutaneous tissue, fibrosarcoma, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										2
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Carcinoma, metastatic, pituitary gland																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Meningioma benign																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+		42
Sciatic, lymphoma malignant mixed																										1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	076	076	079	083	085	093	094	094	094	096	096	096	097	102	104	105	105	105	105	105	105	105	105	105	105
CARCASS ID	563	593	514	571	535	541	522	603	523	513	572	555	601	591	574	553	595	525	542	552	554	564	583	592	605
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X	X																				
Alveolar/bronchiolar adenoma, multiple						X																			
Alveolar/bronchiolar carcinoma				X									X					X							
Fibrosarcoma, metastatic, skin													X												
Hepatocellular carcinoma, metastatic, liver																					X				
Lymphoma malignant histiocytic						X					X					X	X								
Lymphoma malignant lymphocytic	X								X																
Lymphoma malignant mixed															X										
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Mediastinum, lymphoma malignant histiocytic											X														
Mediastinum, lymphoma malignant lymphocytic																									
Mediastinum, lymphoma malignant mixed															X										
Nose	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic	X																								
Lymphoma malignant mixed															X										
Trachea	M	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye						+																			
Harderian gland	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X		X	X			X						X				X			X
Adenoma, multiple																			X						
Carcinoma																									
Bilateral, adenoma					X										X					X			X		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X					X			X			X								
Lymphoma malignant lymphocytic	X				X				X																
Lymphoma malignant mixed															X								X		
Ureter			+			+		+					+			+	+		+		+			+	+
Urinary bladder	M	+	M	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X					X									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed															X										

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	5111	5211	5244	5331	5332	5433	5733	5881	5884	5994	6002	5112	5115	5333	5334	5444	5445	5551	5611	5622	5655	5755	5822	5855	6004	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma															X			X		X				X		6
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma						X			X							X							X			7
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																										4
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinum, lymphoma malignant histiocytic																										1
Mediastinum, lymphoma malignant lymphocytic													X													1
Mediastinum, lymphoma malig. mixed																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Ear										+																1
Eye		+																								2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X	X																			X	X		X	12
Adenoma, multiple																										1
Carcinoma											X										X					2
Bilateral, adenoma	X			X									X													7
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										4
Lymphoma malignant lymphocytic													X				X									5
Lymphoma malignant mixed			X									X												X		5
Ureter	+	+	+		+		+		+	+	+			+	+		+		+		+	+	+	+		26
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																	X									1
Lymphoma malignant mixed																										1

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	25 mg/kg	50 mg/kg
Harderian Gland: Adenoma			
Overall Rates (a)	5/47 (11%)	8/45 (18%)	20/48 (42%)
Adjusted Rates (b)	12.5%	25.0%	49.1%
Terminal Rates (c)	5/40 (13%)	8/32 (25%)	13/33 (39%)
Day of First Observation	731	731	589
Life Table Tests (d)	P<0.001	P=0.146	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.146	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.248	P<0.001
Harderian Gland: Carcinoma			
Overall Rates (a)	0/47 (0%)	3/45 (7%)	2/48 (4%)
Adjusted Rates (b)	0.0%	8.8%	6.1%
Terminal Rates (c)	0/40 (0%)	2/32 (6%)	2/33 (6%)
Day of First Observation		710	731
Life Table Tests (d)	P=0.161	P=0.090	P=0.197
Logistic Regression Tests (d)	P=0.174	P=0.096	P=0.197
Cochran-Armitage Trend Test (d)	P=0.209		
Fisher Exact Test (d)		P=0.113	P=0.253
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/47 (11%)	11/45 (24%)	22/48 (46%)
Adjusted Rates (b)	12.5%	33.1%	54.2%
Terminal Rates (c)	5/40 (13%)	10/32 (31%)	15/33 (45%)
Day of First Observation	731	710	589
Life Table Tests (d)	P<0.001	P=0.030	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.031	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.070	P<0.001
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	17/49 (35%)
Adjusted Rates (b)	7.3%	10.4%	48.2%
Terminal Rates (c)	3/41 (7%)	2/35 (6%)	15/33 (45%)
Day of First Observation	731	616	653
Life Table Tests (d)	P<0.001	P=0.423	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.487	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.500	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	6.7%	8.6%	6.1%
Terminal Rates (c)	1/41 (2%)	3/35 (9%)	2/33 (6%)
Day of First Observation	675	731	731
Life Table Tests (d)	P=0.514N	P=0.590	P=0.595N
Logistic Regression Tests (d)	P=0.461N	P=0.639	P=0.528N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.661N	P=0.510N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	7/50 (14%)	17/49 (35%)
Adjusted Rates (b)	13.7%	18.5%	48.2%
Terminal Rates (c)	4/41 (10%)	5/35 (14%)	15/33 (45%)
Day of First Observation	675	616	653
Life Table Tests (d)	P=0.001	P=0.392	P=0.002
Logistic Regression Tests (d)	P=0.002	P=0.472	P=0.003
Cochran-Armitage Trend Test (d)	P=0.004		
Fisher Exact Test (d)		P=0.500	P=0.007

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	7/49 (14%)
Adjusted Rates (b)	9.8%	10.8%	17.9%
Terminal Rates (c)	4/41 (10%)	2/35 (6%)	4/33 (12%)
Day of First Observation	731	710	580
Life Table Tests (d)	P=0.135	P=0.554	P=0.176
Logistic Regression Tests (d)	P=0.194	P=0.584	P=0.272
Cochran-Armitage Trend Test (d)	P=0.193		
Fisher Exact Test (d)		P=0.643N	P=0.251
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	7/49 (14%)
Adjusted Rates (b)	4.9%	13.2%	19.2%
Terminal Rates (c)	2/41 (5%)	4/35 (11%)	5/33 (15%)
Day of First Observation	731	421	580
Life Table Tests (d)	P=0.034	P=0.167	P=0.045
Logistic Regression Tests (d)	P=0.061	P=0.243	P=0.076
Cochran-Armitage Trend Test (d)	P=0.057		
Fisher Exact Test (d)		P=0.218	P=0.075
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	8/50 (16%)	13/49 (27%)
Adjusted Rates (b)	14.6%	20.6%	33.8%
Terminal Rates (c)	6/41 (15%)	5/35 (14%)	9/33 (27%)
Day of First Observation	731	421	580
Life Table Tests (d)	P=0.019	P=0.284	P=0.025
Logistic Regression Tests (d)	P=0.042	P=0.387	P=0.057
Cochran-Armitage Trend Test (d)	P=0.041		
Fisher Exact Test (d)		P=0.387	P=0.056
Mammary Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	4.9%	9.5%	0.0%
Terminal Rates (c)	2/41 (5%)	0/35 (0%)	0/33 (0%)
Day of First Observation	731	616	
Life Table Tests (d)	P=0.285N	P=0.287	P=0.287N
Logistic Regression Tests (d)	P=0.216N	P=0.358	P=0.287N
Cochran-Armitage Trend Test (d)	P=0.228N		
Fisher Exact Test (d)		P=0.339	P=0.253N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	7.1%	9.5%	0.0%
Terminal Rates (c)	2/41 (5%)	0/35 (0%)	0/33 (0%)
Day of First Observation	716	616	
Life Table Tests (d)	P=0.169N	P=0.431	P=0.161N
Logistic Regression Tests (d)	P=0.115N	P=0.521	P=0.143N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.500	P=0.125N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	7.1%	9.5%	2.6%
Terminal Rates (c)	2/41 (5%)	0/35 (0%)	0/33 (0%)
Day of First Observation	716	616	674
Life Table Tests (d)	P=0.332N	P=0.431	P=0.383N
Logistic Regression Tests (d)	P=0.246N	P=0.521	P=0.317N
Cochran-Armitage Trend Test (d)	P=0.259N		
Fisher Exact Test (d)		P=0.500	P=0.316N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Ovary: Granulosa Cell Tumor			
Overall Rates (a)	0/50 (0%)	5/45 (11%)	5/47 (11%)
Adjusted Rates (b)	0.0%	16.1%	15.6%
Terminal Rates (c)	0/41 (0%)	5/31 (16%)	5/32 (16%)
Day of First Observation		731	731
Life Table Tests (d)	P=0.017	P=0.015	P=0.016
Logistic Regression Tests (d)	P=0.017	P=0.015	P=0.016
Cochran-Armitage Trend Test (d)	P=0.031		
Fisher Exact Test (d)		P=0.021	P=0.024
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	13/49 (27%)	(e) 5/14 (36%)	4/43 (9%)
Adjusted Rates (b)	30.1%		12.5%
Terminal Rates (c)	11/41 (27%)		4/32 (13%)
Day of First Observation	690		731
Life Table Test (d)			P=0.055N
Logistic Regression Test (d)			P=0.046N
Fisher Exact Test (d)			P=0.030N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	5/49 (10%)
Adjusted Rates (b)	4.6%	4.8%	13.8%
Terminal Rates (c)	1/41 (2%)	1/35 (3%)	3/33 (9%)
Day of First Observation	690	347	672
Life Table Tests (d)	P=0.103	P=0.653	P=0.147
Logistic Regression Tests (d)	P=0.152	P=0.508N	P=0.208
Cochran-Armitage Trend Test (d)	P=0.140		
Fisher Exact Test (d)		P=0.691N	P=0.210
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	4/48 (8%)	(e) 0/6 (0%)	3/48 (6%)
Adjusted Rates (b)	9.4%		9.4%
Terminal Rates (c)	3/40 (7%)		3/32 (9%)
Day of First Observation	655		731
Life Table Test (d)			P=0.613N
Logistic Regression Test (d)			P=0.537N
Fisher Exact Test (d)			P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	(e,f) 5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	9.3%		3.0%
Terminal Rates (c)	3/41 (7%)		1/33 (3%)
Day of First Observation	675		731
Life Table Test (d)			P=0.254N
Logistic Regression Test (d)			P=0.202N
Fisher Exact Test (d)			P=0.187N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	5/50 (10%)	(e,f) 6/50 (12%)	1/49 (2%)
Adjusted Rates (b)	11.7%		3.0%
Terminal Rates (c)	4/41 (10%)		1/33 (3%)
Day of First Observation	675		731
Life Table Test (d)			P=0.163N
Logistic Regression Test (d)			P=0.124N
Fisher Exact Test (d)			P=0.107N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	(e,f) 11/50 (22%)	21/49 (43%)
Adjusted Rates (b)	35.4%		48.4%
Terminal Rates (c)	12/41 (29%)		11/33 (33%)
Day of First Observation	655		527
Life Table Test (d)			P=0.086
Logistic Regression Test (d)			P=0.179
Fisher Exact Test (d)			P=0.182

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) Nineteen spleens were examined microscopically.

TABLE D4a. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN CONTROL FEMALE $B6C3F_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	6/50	0/50	6/50
Chlorpheniramine maleate (c)	2/50	0/50	2/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	0/50	0/50	0/50
Malonaldehyde, sodium salt (c)	0/50	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50	(d) 2/50	(d) 2/50
Methyl carbamate (e)	1/50	0/50	1/50
Chlorinated trisodium phosphate (b)	0/50	1/50	1/50
TOTAL	9/350 (2.6%)	3/350 (0.9%)	12/350 (3.4%)
SD (f)	4.43%	1.57%	4.12%
Range (g)			
High	6/50	2/50	6/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	(h) 41/2,040 (2.0%)	(i) 7/2,040 (0.3%)	(h,i) 48/2,040 (2.4%)
SD (f)	2.06%	0.88%	2.19%
Range (g)			
High	4/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Papillary adenocarcinomas
(e) Study performed at Microbiological Associates
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes three papillary adenomas, one cystadenoma, NOS, and two papillary cystadenomas, NOS
(i) Includes one adenocarcinoma, NOS, two papillary adenocarcinomas, and one papillary cystadenocarcinoma, NOS

TABLE D4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	0/50	0/50	0/50
Chlorpheniramine maleate (c)	4/50	2/50	6/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	3/49	1/49	4/49
Malonaldehyde, sodium salt (c)	0/50	2/50	2/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	5/50	3/50	7/50
Methyl carbamate (d)	4/49	1/49	4/49
Chlorinated trisodium phosphate (b)	6/50	0/50	6/50
TOTAL	22/348 (6.3%)	9/348 (2.6%)	29/348 (8.3%)
SD (e)	4.69%	2.22%	4.95%
Range (f)			
High	6/50	3/50	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls			
TOTAL	107/2,032 (5.3%)	(g) 81/2,032 (4.0%)	184/2,032 (9.1%)
SD (e)	4.34%	2.42%	4.70%
Range (f)			
High	9/49	4/48	10/49
Low	0/50	0/50	1/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) A hepatoblastoma was also observed.

TABLE D4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN CONTROL FEMALE $B6C3F_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	3/50	1/50	4/50
Chlorpheniramine maleate (c)	5/50	1/50	6/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	3/50	0/50	3/50
Malonaldehyde, sodium salt (c)	4/50	1/50	5/50
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	1/50	1/50	2/50
Methyl carbamate (d)	6/49	1/49	7/49
Chlorinated trisodium phosphate (b)	3/50	3/50	6/50
TOTAL	25/349 (7.2%)	8/349 (2.3%)	33/349 (9.5%)
SD (e)	3.30%	1.80%	3.66%
Range (f)			
High	6/49	3/50	7/49
Low	1/50	0/50	2/50
Overall Historical Incidence for Untreated Controls			
TOTAL	101/2,026 (5.0%)	45/2,026 (2.2%)	145/2,026 (7.2%)
SD (e)	3.65%	1.78%	4.21%
Range (f)			
High	7/50	3/50	8/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE D4d. HISTORICAL INCIDENCE OF OVARIAN GRANULOSA CELL TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls
Historical Incidence for All Water Gavage Vehicle Controls	
Iodinated glycerol (b)	0/48
Chlorpheniramine maleate (c)	(d) 1/50
Tetrakis(hydroxymethyl)phosphonium chloride (c)	(d) 1/50
Malonaldehyde, sodium salt (c)	0/44
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50
Methyl carbamate (e)	0/49
Chlorinated trisodium phosphate (b)	0/48
TOTAL	2/339 (0.6%)
SD (f)	0.98%
Range (g)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls	
TOTAL	(h) 13/1,867 (0.7%)
SD (f)	1.50%
Range (g)	
High	3/47
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Luteoma
(e) Study performed at Microbiological Associates
(f) Standard deviation
(g) Range and SD are presented for groups of 35 or more animals.
(h) Includes four luteomas and one granulosa cell carcinonoma

TABLE D4e. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls	
	Papilloma	Papilloma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls		
Iodinated glycerol (b)	1/49	1/49
Chlorpheniramine maleate (c)	0/48	0/48
Tetrakis(hydroxymethyl)phosphonium chloride (c)	2/49	2/49
Malonaldehyde, sodium salt (c)	1/46	1/46
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	0/50	0/50
Methyl carbamate (d)	0/47	0/47
Chlorinated trisodium phosphate (b)	0/50	0/50
TOTAL	4/339 (1.2%)	4/339 (1.2%)
SD (e)	1.62%	1.62%
Range (f)		
High	2/49	2/49
Low	0/50	0/50
Overall Historical Incidence for Untreated Controls		
TOTAL	(g) 17/1,994 (0.9%)	(g) 18/1,994 (0.9%)
SD (e)	1.56%	1.75%
Range (f)		
High	3/50	4/50
Low	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes one papilloma, NOS, and three diagnoses of papillomatosis

TABLE D4f. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for All Water Gavage Vehicle Controls			
Iodinated glycerol (b)	4/46	1/46	5/46
Chlorpheniramine maleate (c)	5/46	0/46	5/46
Tetrakis(hydroxymethyl)phosphonium chloride (c)	11/50	0/50	11/50
Malonaldehyde, sodium salt (c)	2/43	0/43	2/43
Tetrakis(hydroxymethyl)phosphonium sulfate (c)	8/43	0/43	8/43
Methyl carbamate (d)	9/49	0/49	9/49
Chlorinated trisodium phosphate (b)	8/45	0/45	8/45
TOTAL	47/322 (14.6%)	1/322 (0.3%)	48/322 (14.9%)
SD (e)	6.36%	0.82%	6.08%
Range (f)			
High	11/50	1/46	11/50
Low	2/43	0/50	2/43
Overall Historical Incidence for Untreated Controls			
TOTAL	(g) 231/1,782 (13.0%)	(h) 13/1,782 (0.7%)	(g,h) 244/1,782 (13.7%)
SD (e)	10.20%	1.34%	10.58%
Range (f)			
High	18/49	3/50	19/49
Low	0/48	0/49	0/48

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Study performed at EG&G Mason Research Institute
(c) Study performed at Battelle Columbus Laboratories
(d) Study performed at Microbiological Associates
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.
(g) Includes eight chromophobe adenomas
(h) Includes three adenocarcinomas, NOS, and one chromophobe carcinoma

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	49
ALIMENTARY SYSTEM			
Intestine large, colon	(45)	(6)	(44)
Infarct			1 (2%)
Parasite metazoan			1 (2%)
Intestine large, rectum	(46)	(6)	(43)
Parasite metazoan			1 (2%)
Intestine small, duodenum	(44)	(5)	(41)
Inflammation, chronic active		1 (20%)	
Ulcer		1 (20%)	
Intestine small, ileum	(44)	(4)	(43)
Inflammation, necrotizing			1 (2%)
Intestine small, jejunum	(45)	(4)	(42)
Necrosis, coagulative			1 (2%)
Liver	(50)	(50)	(49)
Amyloid deposition		1 (2%)	
Angiectasis	1 (2%)		1 (2%)
Atypical cells		2 (4%)	
Clear cell focus			2 (4%)
Degeneration, cystic		1 (2%)	
Hematopoietic cell proliferation		4 (8%)	2 (4%)
Infiltration cellular, lymphocytic		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic active	2 (4%)		
Leukocytosis	1 (2%)	2 (4%)	1 (2%)
Necrosis, coagulative		4 (8%)	3 (6%)
Pigmentation, hematoidin			1 (2%)
Pigmentation, hemosiderin			1 (2%)
Vacuolization cytoplasmic	1 (2%)		2 (4%)
Artery, necrosis, fibrinoid	1 (2%)		
Bile duct, cyst			1 (2%)
Mesentery	(48)	(6)	(47)
Inflammation, chronic active	2 (4%)		1 (2%)
Necrosis			2 (4%)
Thrombus			2 (4%)
Pancreas	(50)	(6)	(47)
Inflammation, chronic active			2 (4%)
Acinus, atrophy	3 (6%)	1 (17%)	4 (9%)
Duct, ectasia	1 (2%)		
Stomach, forestomach	(46)	(6)	(44)
Acanthosis	3 (7%)		5 (11%)
Hyperkeratosis	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Stomach, glandular	(47)	(5)	(44)
Inflammation, chronic active	1 (2%)		1 (2%)
Tooth	(50)	(6)	(48)
Dysplasia	1 (2%)		3 (6%)
Foreign body			1 (2%)
Inflammation, chronic active	2 (4%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(6)	(49)
Cardiomyopathy, chronic	1 (2%)		4 (8%)
Inflammation, chronic active			2 (4%)
Mineralization			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(7)	(48)
Corticomedullary junction, degeneration, fatty			1 (2%)
Adrenal gland, cortex	(50)	(6)	(47)
Accessory adrenal cortical nodule			3 (6%)
Cyst			1 (2%)
Hematopoietic cell proliferation		2 (33%)	1 (2%)
Hyperplasia	1 (2%)		
Hypertrophy	1 (2%)		
Adrenal gland, medulla	(50)	(6)	(48)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia	5 (10%)		2 (4%)
Islets, pancreatic	(50)	(6)	(47)
Hyperplasia			2 (4%)
Parathyroid gland	(31)	(5)	(28)
Cyst			1 (4%)
Pituitary gland	(49)	(14)	(43)
Pars distalis, cyst	1 (2%)		
Pars distalis, hyperplasia	22 (45%)	4 (29%)	13 (30%)
Thyroid gland	(48)	(6)	(48)
Inflammation, chronic active	2 (4%)		1 (2%)
C-cell, hyperplasia	1 (2%)		1 (2%)
Follicle, cyst	1 (2%)		3 (6%)
Follicular cell, hyperplasia	9 (19%)		11 (23%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(50)	(45)	(47)
Atrophy	3 (6%)	39 (87%)	38 (81%)
Cyst	10 (20%)	9 (20%)	6 (13%)
Hemorrhage, acute			2 (4%)
Inflammation, suppurative	1 (2%)		1 (2%)
Mineralization	1 (2%)		1 (2%)
Thrombus			1 (2%)
Uterus	(50)	(35)	(49)
Dilatation		2 (6%)	4 (8%)
Hemorrhage		5 (14%)	1 (2%)
Inflammation, suppurative	1 (2%)		2 (4%)
Thrombus	1 (2%)		
Artery, hyperplasia, cystic, glandular		1 (3%)	
Endometrium, hyperplasia, cystic, glandular	47 (94%)	31 (89%)	45 (92%)
HEMATOPOIETIC SYSTEM			
Blood		(2)	
Neutrophilia		2 (100%)	
Bone marrow	(50)	(6)	(48)
Femoral, hyperplasia		2 (33%)	1 (2%)
Femoral, hyperplasia, reticulum cell	1 (2%)		
Femoral, myelofibrosis	3 (6%)		1 (2%)
Vertebral, hyperplasia			1 (2%)
Vertebral, myelofibrosis	29 (58%)		10 (21%)
Lymph node	(50)	(13)	(46)
Iliac, thrombus			1 (2%)
Lumbar, hyperplasia, lymphoid	1 (2%)		
Mandibular, hematopoietic cell proliferation		2 (15%)	1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	(13)	(46)
Mandibular, hyperplasia, plasma cell			3 (7%)
Mandibular, infiltration cellular, histiocytic			1 (2%)
Renal, hyperplasia, lymphoid		1 (8%)	
Renal, thrombus			1 (2%)
Lymph node, mesenteric	(11)	(7)	(13)
Angiectasis			3 (23%)
Hematopoietic cell proliferation	1 (9%)	1 (14%)	
Hyperplasia, lymphoid		1 (14%)	
Hyperplasia, plasma cell			1 (8%)
Thrombus			1 (8%)
Spleen	(50)	(19)	(48)
Cyst	1 (2%)		
Hematopoietic cell proliferation	15 (30%)	10 (53%)	40 (83%)
Hyperplasia, lymphoid		1 (5%)	
Infarct			1 (2%)
Thymus	(48)	(4)	(38)
Cyst	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(29)	(48)	(33)
Hyperplasia	1 (3%)		
Hyperplasia, cystic	20 (69%)	40 (83%)	29 (88%)
Skin	(50)	(14)	(48)
Abscess		1 (7%)	
Alopecia		1 (7%)	
Foreign body		1 (7%)	1 (2%)
Inflammation, chronic active		1 (7%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(50)	(6)	(48)
Fibrosis, focal			1 (2%)
Hemorrhage, acute	1 (2%)		
Inflammation, chronic active	2 (4%)		
Artery, necrosis, fibrinoid	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(7)	(48)
Hemorrhage, acute			1 (2%)
Inflammation, chronic	1 (2%)		
Peripheral nerve	(47)	(43)	(42)
Sciatic, degeneration		4 (9%)	
Spinal cord	(50)	(6)	(49)
White matter, degeneration	5 (10%)	1 (17%)	1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(49)
Hemorrhage, acute		1 (2%)	1 (2%)
Inflammation, chronic	12 (24%)	28 (56%)	14 (29%)
Pigmentation, hemosiderin			3 (6%)
Alveolar epithelium, hyperplasia	8 (16%)	26 (52%)	17 (35%)
Nose	(50)	(6)	(48)
Inflammation, chronic active			1 (2%)
Nasolacrimal duct, foreign body			1 (2%)
Nasolacrimal duct, granuloma			1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)		5 (10%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N*-METHYLOLACRYLAMIDE (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Eye			(2)
Lens, cataract			2 (100%)
Retina, atrophy			2 (100%)
Harderian gland	(47)	(45)	(48)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(11)	(48)
Amyloid deposition		1 (9%)	
Atrophy		1 (9%)	
Hydronephrosis			1 (2%)
Infarct			5 (10%)
Inflammation		1 (9%)	
Metaplasia, osseous	2 (4%)		3 (6%)
Mineralization			1 (2%)
Necrosis			1 (2%)
Nephropathy, chronic	10 (20%)	3 (27%)	23 (48%)
Renal tubule, regeneration			1 (2%)
Urinary bladder	(43)	(6)	(47)
Hemorrhage		1 (17%)	
Inflammation, chronic active	1 (2%)		

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6 and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) (6,18 mo) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (18 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (6 mo)	MHV (mouse hepatitis virus) GDVII (24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus) (6 mo)	RCV/SDA (sialodacryoadenitis virus) (18,24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N*-METHYLOLACRYLAMIDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	KRV
18	1/10	KRV
	10/10	Sendai
24	1/10	KRV
	7/10	Sendai
MICE		
6	2/10	MHV
18	7/10	Sendai

(a) Blood samples were taken from sentinel animals at 6 and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX F

BEHAVIORAL TESTING PROCEDURES

APPENDIX F. BEHAVIORAL TESTING PROCEDURES

The behavioral tests were performed during the sixth week of dosing (rats: August 19-21, 1981; mice: August 25-28, 1981) and again on the same animals during the last week of dosing (rats: October 6-9, 1981; mice: October 13-16, 1981) in the 13-week studies. The test battery was performed over a 2-day period--all males during the first 2 days and all females during the next 2 days. Spontaneous motor activity was tested in the morning of the first day, and grip strength was tested in the afternoon. On the second day, startle measurements were taken in the morning and landing foot spread measurements (rats) or rotarod training and testing (mice) in the afternoon. Animals from the different dose groups of the same sex and species, including vehicle controls, were run simultaneously or in mixed sequence so that there were no systematic differences among the animals at time of testing or among the environmental conditions during testing. Dosing was delayed on test days until after testing had been completed so that the influence of any acute pharmacologic effects after dosing was minimized during behavioral testing.

On the day of behavioral testing, animals were transferred to clean cages on a clean rack and transported by elevator from the second to the fourth floor where the Behavioral Testing Laboratory is located. After a brief period of accommodation following transport, one animal from each dose group was placed individually into one of the 21 × 29 cm test cages that were installed inside individual sound-isolating test cubicles for measurement of spontaneous motor activity. The cubicles were darkened, and 80-db "white noise" was introduced through speakers mounted on the cubicle walls. Three photobeam/photoresistor pairs were mounted in U-shaped holder units along the cage sides so that the infrared photobeams divided the cage area approximately into thirds and so that the photobeams were interrupted by animal movement within the cage. Signals from these sensors were fed through Coulbourn Instruments signal-processing equipment to a 10-channel microprocessor-based printer. Activity counts within an individual cage were accumulated silently and totaled separately every 5 minutes during the 20-minute testing session. When the session was over, animals were removed and placed in fresh cages, and the next set of animals was placed in the activity cages.

Grip strength was measured with a device and procedure similar to those described by Meyer et al. (1979). Briefly, the animal was allowed to grip a triangular ring with its forepaws and was gently pulled back along a platform until its grip was broken. As the backward motion continued, its hind paws reached a T-shaped rear-limb grip bar that it was allowed to grasp and then was forced to release by continued pulling. Chatillon push-pull strain gauges were used to record the maximum strain required to break the animal's grip in each case. The average of three valid measurements was taken as the animal's score for either forelimb or hind limb grip strength.

Auditory startle response was measured with a Respondex A Startle Monitor (Columbus Instruments, Columbus, Ohio). This device detects movement as a capacitance change in the electrical field above the sensor. Each animal was placed inside a plastic cage (21.5 × 23.5 × 21.5 cm high) for rats or a clean, covered 1,000-ml beaker for mice which rested on the movement detector inside an Industrial Acoustics sound-isolating cubicle. Fifteen brief (0.4 seconds for rats, 0.2 seconds for mice), intense 7,000-Hz, 124-db auditory stimuli were presented approximately 5-10 seconds apart, and the magnitude of startle response to each stimulus was recorded.

The procedure for measurement of landing foot spread was modeled after that described by Edwards and Parker (1977) for measurement of acrylamide neuropathy in rats. After the hind paws of each rat had been lightly inked, the rat was suspended and dropped a distance of 32 cm onto a white blotter that provided a permanent record of hind foot splay. The distance between the outermost digits on the two hind paws was measured on each test card. The average of three valid measurements was used as the rat's test score.

For rotarod training, mice were placed on a 2.5-cm diameter horizontal wooden dowel that was rotating (rolling) at 12 rpm and elevated approximately 38 cm over cages containing wood chip bedding material. Up to three mice were trained or tested at any one time. Aluminum disks separated the three test areas on the rod. During the 2-minute training period, mice that fell from the rod were replaced as often as necessary. For testing, the mice were placed on the rod, and the total time they remained on the rod was recorded up to a maximum of 2 minutes. Training and testing were separated by approximately 25 minutes.

APPENDIX G

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pelleted Diet: March 1982 to March 1984

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NCI, 1976; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.26 ± 1.04	21.3-26.3	26
Crude fat (percent by weight)	5.07 ± 0.55	3.3-5.7	26
Crude fiber (percent by weight)	3.44 ± 0.51	2.9-5.6	26
Ash (percent by weight)	6.56 ± 0.42	5.7-7.3	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,423 ± 4,794	3,600-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	16.7 ± 3.42	12.0-27.0	26
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.30 ± 0.13	1.11-1.63	26
Phosphorus (percent)	0.97 ± 0.05	0.89-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.51 ± 0.15	0.17-0.77	26
Cadmium (ppm)	<0.10		26
Lead (ppm)	0.76 ± 0.63	0.33-3.37	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.30 ± 0.07	0.13-0.42	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm) (b)	8.66 ± 20.15	0.10-22.00	26
Nitrite nitrogen (ppm) (b)	2.05 ± 2.04	0.10-7.10	26
BHA (ppm) (c)	4.31 ± 4.70	2.00-17.00	26
BHT (ppm) (c)	2.59 ± 2.53	1.00-12.00	26
Aerobic plate count (CFU/g) (d)	40,765 ± 33,607	4,900-130,000	26
Coliform (MPN/g) (e)	46.12 ± 123	3.00-460	26
E. coli (MPN/g)	≤3.00		26
Total nitrosamines (ppb) (f)	5.16 ± 5.84	1.70-30.90	26
N-Nitrosodimethylamine (ppb) (f)	4.13 ± 5.83	0.80-30.00	26
N-Nitrosopyrrolidine (ppb) (f)	1.03 ± 0.25	0.81-1.70	26
Pesticides (ppm)			
α-BHC (a,g)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC-Lindane (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (a)	<0.05		26
Dieldrin (a)	<0.01		26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (h)	0.10 ± 0.09	0.05-0.45	26
Endosulfan I (a)	<0.01		26
Endosulfan II (a)	<0.01		26
Endosulfan sulfate (a)	<0.03		26

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) All values were corrected for percent recovery.
(g) BHC = hexachlorocyclohexane or benzene hexachloride
(h) Fourteen lots contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report No. 352 for the 2-year gavage studies of *N*-methylolacrylamide in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives during September and October 1987 by Dynamac Corporation. The laboratory studies were conducted for the NTP by the Battelle Columbus Laboratories, Columbus, OH. Animal exposures to the chemical in water by gavage began in April 1982. The full audit report is on file at the NIEHS. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, environmental conditions, dosing, masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, and correlations between clinical and mass observations recorded during the last 3 months of life, necropsy observations, and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of animals in all study groups, plus other relevant cases to verify animal identity and to examine for untrimmed potential lesions
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group to examine for proper match and inventory
(8) Comparison of tabulated pathology diagnoses to verify that update changes were made on the final pathology tables

Procedures and events were documented adequately in the archival records with the exception of disposition of surplus animals, rack changes, temperature, and humidity Review of the inlife toxicology data and chemistry data revealed no significant discrepancies. Inspection of wet tissues for individual animal identifiers showed that 65/76 rats and 68/75 mice were identified correctly by their residual tissues. The toxicology and pathology study records for the animals with incorrect or incomplete identification received further review. The results indicated that 10/11 rats and 4/8 mice did not represent misidentification during life or subsequent tissue mixup. The identification discrepancies were related to inconsistent saving of the identifiers. Audit of the data records for the remaining one rat and four mice contained noncorroborative evidence in the toxicology and/or pathology study records. Review of the wet tissues identified 12 untrimmed potential lesions in 12/76 rats and 12 untrimmed potential lesions in 11/75 mice examined. The untrimmed potential lesions were distributed across groups and appeared in various organs. Review of these findings suggested that resolution of these potential lesions would have no impact on the overall study results; therefore, no further action was taken.

In conclusion, the data, documents, and records of the 2-year gavage studies of *N*-methylolacrylamide were considered adequate to support the conclusions presented in the Technical Report.